DRAFT

Report on Carcinogens Background Document for

Glass Wool Fibers

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FOREWORD

The Report on Carcinogens (RoC) is prepared in response to Section 301 of the Public Health Service Act as amended. The RoC contains a list of identified substances (i) that either are known to be human carcinogens or are reasonably be anticipated to be human carcinogens and (ii) to which a significant number of persons residing in the United States are exposed. The Secretary, Department of Health and Human Services (HHS), has delegated responsibility for preparation of the RoC to the National Toxicology Program (NTP), which prepares the report with assistance from other Federal health and regulatory agencies and nongovernmental institutions.

Nominations for (1) listing a new substance, (2) reclassifying the listing status for a substance already listed, or (3) removing a substance already listed in the RoC are reviewed in a multi-step, scientific review process with multiple opportunities for public comment. The scientific peer-review groups evaluate and make independent recommendations for each nomination according to specific RoC listing criteria. This background document was prepared to assist in the review of glass wool. The scientific information used to prepare Sections 3 through 5 of this document must come from publicly available, peer-reviewed sources. Information in Sections 1 and 2, including chemical and physical properties, analytical methods, production, use, and occurrence may come from published and/or unpublished sources. The NTP will provide a reference for all published and unpublished sources used in this document. For each study cited in the background document from the peer-reviewed literature, information on funding sources (if available) and the authors' affiliations will be provided in the reference section. Any interpretive conclusions, comments, or statistical calculations made by the authors or peer reviewers of this document that are not contained in the original citation are identified in brackets [ ]. This draft document will be peer reviewed in a public forum by an *ad hoc* expert panel of scientists from public and private sectors with relevant expertise and knowledge selected by the NTP in accordance with the Federal Advisory Committee Act and HHS guidelines and regulations. This document will be finalized based on the peer-review recommendations of the expert panel and public comments received for this draft document.

A detailed description of the RoC nomination review process and a list of all substances under consideration for listing in or delisting from the RoC can be obtained by accessing the 12th RoC at http://ntp.niehs.nih.gov/go/9732. The most recent RoC, the 11th Edition (2004), is available at http://ntp.niehs.nih.gov/go/19914.

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Criteria for Listing Agents, Substances or Mixtures in the Report on Carcinogens

U.S. Department of Health and Human Services

National Toxicology Program

The criteria for listing an agent, substance, mixture, or exposure circumstance in the RoC are as follows:

Known To Be Human Carcinogen:

There is sufficient evidence of carcinogenicity from studies in humans*, which indicates a causal relationship between exposure to the agent, substance, or mixture, and human cancer.

Reasonably Anticipated To Be Human Carcinogen:

There is limited evidence of carcinogenicity from studies in humans*, which indicates that causal interpretation is credible, but that alternative explanations, such as chance, bias, or confounding factors, could not adequately be excluded,

or

there is sufficient evidence of carcinogenicity from studies in experimental animals, which indicates there is an increased incidence of malignant and/or a combination of malignant and benign tumors (1) in multiple species or at multiple tissue sites, or (2) by multiple routes of exposure, or (3) to an unusual degree with regard to incidence, site, or type of tumor, or age at onset,

or

there is less than sufficient evidence of carcinogenicity in humans or laboratory animals; however, the agent, substance, or mixture belongs to a well-defined, structurally related class of substances whose members are listed in a previous Report on Carcinogens as either known to be a human carcinogen or reasonably anticipated to be a human carcinogen, or there is convincing relevant information that the agent acts through mechanisms indicating it would likely cause cancer in humans.

Conclusions regarding carcinogenicity in humans or experimental animals are based on scientific judgment, with consideration given to all relevant information. Relevant information includes, but is not limited to, dose response, route of exposure, chemical structure, metabolism, pharmacokinetics, sensitive sub-populations, genetic effects, or other data relating to mechanism of action or factors that may be unique to a given substance. For example, there may be substances for which there is evidence of carcinogenicity in laboratory animals, but there are compelling data indicating that the agent acts through mechanisms which do not operate in humans and would therefore not reasonably be anticipated to cause cancer in humans.

*This evidence can include traditional cancer epidemiology studies, data from clinical studies, and/or data derived from the study of tissues or cells from humans exposed to the substance in question that can be useful for evaluating whether a relevant cancer mechanism is operating in people.

Executive Summary

Introduction

Glass is an amorphous material produced by solidification from a molten state without crystallization and containing a glass former that can be melted and quenched into a glassy state. Silicon dioxide is the major glass former used for commercial applications. Glass wool refers to fine glass fibers forming a mass resembling wool and most commonly used for insulation and filtration. Glass wool fibers were first introduced into commerce in the 1930s and are now among the world's most extensively used insulating materials. Special-purpose fibers make up a small fraction of the market and are used, as the name implies, in specialized applications.

Glass wool fiber diameters vary within a product but follow an approximately log-normal distribution. The fiber diameter is controlled by the manufacturing process. Unlike crystalline fibers, such as asbestos, glass fibers do not split lengthwise into fibers with smaller diameters, but only break across the fiber resulting in shorter fibers with the same diameter.

There are considerable differences in the chemical compositions and physical characteristics of glass fibers, which may influence the toxicity and potential carcinogenicity of the fibers. Fibers have also been examined based upon other characteristics, including biopersistence, retention and clearance rates, and biodurability. The European Union (EU) and Germany have established criteria for labeling and classifying synthetic vitreous fibers (SVF) based on their potential human health hazard.

Human Exposure

The vast majority of SVF produced and used in the United States consists of glass wool used for home and building insulation. Small amounts of glass fibers are produced for special applications such as use in battery separator media, high-efficiency filters, and aircraft insulation. Glass wool is produced by heating the glass to high temperatures, extruding the molten glass to form small streams of glass fibers, and using centrifugal force to attenuate the streams of glass into glass fibers. Finer fibers are formed by flame

attenuation. Most general purpose insulation glass wools have nominal diameters ranging from 1 to 10 μm, while special-purpose fibers generally range from 0.1 to 3 μm; however, product bulk samples may have fibers with diameters that are several times greater or smaller than the nominal diameters. ACGIH noted that because of this variation, all wool fiber products contain respirable fibers. The physical properties of fibers affect their likelihood of becoming airborne, with smaller fibers more likely to become airborne. Because of this, the average diameter and length may be smaller and the percentage of respirable fibers higher for airborne fibers compared with the bulk product.

Occupational exposure may occur in manufacturing facilities and as well as for end-users, such as during installation, removal, fabrication, or otherwise working with glass wool outside the manufacturing environment (end-use). OSHA has estimated that more than 225,000 workers in the United States are exposed to synthetic mineral fibers in manufacturing and end-use applications. General population exposure may occur from exposure to SVFs from insulation and building materials or from fibers in the air near manufacturing facilities or areas near building fires or implosions. Exposure may also occur during do-it-yourself home remodeling activities.

No traditional biological indices of exposure exist for SVFs, although the measurement of fibers in human lung tissue has been attempted as a means to assess exposure to SVFs. In addition, a recent study investigated the use of nasal lavage as a biomonitoring method for SVFs.

Fine mineral fiber emissions are regulated by the EPA, respirable fibers ("particulates not otherwise regulated") are regulated by OSHA; ACGIH, NIOSH, and OSHA have set guidelines for fibers in the air in the workplace.

Human Cancer Studies

A number of epidemiological studies have evaluated the relationship between glass wool exposure and cancer in humans. The studies fall into three main groups: (1) cohort and case-control studies of workers in SVF manufacture; (2) cohort or case-control studies of

workers exposed in glass wool applications (e.g., insulators and construction workers); and (3) population-based case-control studies.

Studies within the SVF manufacturing industry have attempted to distinguish between exposure to different types of SVF, and the large cohort and nested case-control studies of workers exposed in plants predominantly engaged in glass wool manufacture are the most informative. [The principal limitations of the glass wool cohort and case-control studies of manufacturing workers include potential misclassification of exposure, particularly for past exposures for which few monitoring data are available, inadequate length of follow-up in some studies for cancers of longer latency, potential confounding by smoking or co-exposure to other chemicals, and possible misdiagnosis or inadequate ascertainment of some cancer outcomes, such as mesothelioma. In contrast, studies of workers in SVF applications (two cohort studies and three case-control studies of respiratory cancer) and the population-based case-control studies or cancer registry studies (cancers of the respiratory and/or gastrointestinal tract, non-Hodgkin's lymphoma, breast, colon, ovary and rectum) have generally been unable to distinguish between types of fibers and are consequently less informative, although intermittent exposures may be higher than observed among manufacturing workers (IARC, 2002). In addition, these studies generally have small numbers of potentially glass wool-exposed subjects and shorter follow-up times than studies of manufacturing workers, and thus limited statistical power to detect long-term effects.]

Cancer mortality or incidence has been studied in four cohorts of manufacturing workers: (1) a combined cohort of male and female U.S. SVF manufacturing workers including five plants making mostly glass wool and three making glass wool and filament (Marsh *et al.* 2001a, Stone *et al.* 2004); (2) a combined cohort of male and female manufacturing workers in five European glass wool plants (Boffetta *et al.* 1997, 1999); (3) a cohort of male manufacturing workers in Canada (Shannon *et al.* 2005); and (4) a cohort of male manufacturing workers in France (Moulin *et al.* 1986). The cohorts of manufacturing workers in the United States and Europe are the largest studies and have adequate follow-up to detect cancers with longer latencies (220,700 person-years of exposure in the U.S. cohort and approximately 201,000 person-years of exposure in the European cohort). In

both cohorts, several earlier studies of subcohorts have been conducted, together with two nested case-control studies of respiratory cancer in the U.S. cohort (Marsh *et al*. 2001a, and Chiazze *et al.* 1992, 1993) and one of lung cancer from part of the European cohort (Gardner *et al*. 1988).

Reconstruction of glass wool exposures indicated that measurable exposure to respirable glass wool fibers occurred among production workers, and that exposure was higher in the earlier periods of operations. However, as the Interanational Agency for Research on Cancer (IARC) (2002) noted, the concentrations of fibers to which production workers were exposed were generally low.

The potential effect of glass wool exposure on lung and upper respiratory tract cancers has been studied most extensively, due to the structural similarity between glass wool, other SVFs, and asbestos. Findings for respiratory cancers and other tumor sites of interest are discussed below.

Respiratory cancers

Significant increases in respiratory cancer mortality were observed among glass wool-exposed workers in unadjusted analyses in U.S. (SMR = 1.18, 95% CI = 1.04 to 1.34, lung + larynx, compared with local rates) (Marsh *et al.* 2001a), European (SMR = 1.27, 95% CI = 1.07 to 1.50, lung only, compared with national rates) (Boffetta *et al.* 1997), and Canadian workers (SMR = 1.63, 95% CI = 1.18 to 2.21, lung only, compared with regional rates) (Shannon *et al.* 2005). Among female workers in the U.S. cohort, no increase in respiratory cancer (trachea, bronchus and lung) was observed in the whole cohort compared with national or local mortality rates, but in an internal analysis of glass wool-only vs. filament only-exposed workers, a significant 3-fold increase in these cancers was observed (RR = 3.24, 95% CI = 1.27 to 8.28) (Stone *et al.* 2004). Excesses of lung cancer incidence were observed among the European workers (SIR = 1.28, 95% CI = 0.91 to 1.74, compared with national rates) (Boffetta *et al.* 1999) and Canadian workers (SIR =1.60, 95% CI = 1.19 to 2.11, compared to regional rates) (Shannon *et al*. 2005), but not among French workers (SIR = 0.74, 95% CI = 0.24 to 1.72, compared with regional rates) (Moulin *et al.* 1986).

Attempts were made to control for the effects of smoking and other potentially confounding exposures, including asbestos, formaldehyde and silica, in the nested case-control study of the U.S. cohort. Adjusting for ever/never smoking (using data obtained from a sample of proxies) reduced the risk of lung cancer mortality among U.S. glass wool workers to nonsignificance. (Formaldehyde exposure was also independently associated with lung cancer in this cohort, but models for glass wool and lung cancer adjusting for both formaldehyde and smoking were not presented.) The available data on these and other potentially confounding exposures have been insufficient to adequately control for them in the European, Canadian, and French studies.

Several studies evaluated exposure-response relationships. In the U.S. cohort and case-control studies, no clear exposure-response relationships with duration of exposure or cumulative exposure were observed. An association between average intensity of exposure was observed in an unadjusted model but not in models adjusted for smoking or other confounders or in weighted-exposure models (Marsh *et al*. 2001a, Stone *et al*. 2001, Youk *et al*. 2001). There was a modest trend towards increased risk with longer time since first hire in the U.S. but not the European cohort. Similarly, in the nested case-control studies of lung cancer among the U.K. subgroup of the European cohorts, no significant exposure-response relationships with lung cancer were observed, with the exception of a significant increase among glass wool and/or superfine fiber-exposed workers after 10 to 19 years since first hire (Gardner *et al.* 1988). In the Canadian cohort, there was some evidence of a trend towards increased risk with longer duration of employment, time since first hire, and year of hire (Shannon *et al.* 2005).

In the two cohort and three case-control studies of lung cancer among construction and other application workers, and in the population-based, case-control studies of lung cancer, no significant increases in lung cancer risk were observed. [Glass wool exposure cannot be distinguished from other SVF exposure in these studies, and few attempts to adjust for smoking and other confounders were conducted.]

With respect to mesothelioma, only one death was observed among glass wool-exposed workers in the European cohort (Boffetta *et al.* 1997). Marsh *et al.* (2001b) observed 8

possible deaths from malignant mesothelioma among the glass wool or filament-exposed workers, but a review of pathology reports or medical records, which were available for only four of these cases, showed that at least one of them was a misdiagnosis. When either a broad (including benign tumors) or more strict coding scheme for mesothelioma was used, a deficit of cases was observed among glass wool-exposed workers relative to expected rates, according to the authors. An earlier case-control study by Rödelsperger *et al.* (2001) reported a significant 3-fold increase in risk of mesothelioma after adjustment for asbestos and other potential confounders, and a significant 2-fold increase in pleural mesothelioma incidence was observed among a cohort of construction workers by Engholm *et al.* (1987), but confounding by asbestos may have occurred in these studies.

Upper respiratory cancers

Marsh *et al.* (2001a) did not report these cancers separately for the glass wool-exposed workers, but nonsignificant increases in these cancers were observed in the combined (glass wool- and filament-exposed) cohort. In the European cohort, a nonsignificant increase in oral, pharyngeal, and laryngeal mortality and incidence was observed among glass wool-exposed workers (Boffetta *et al.* 1997, 1999). Moulin *et al.* (1986) reported a significant excess of "upper respiratory and alimentary tract" cancers in the French cohort, and Marchand *et al.* (2000) reported nonsignificant increases in laryngeal and hypopharyngeal cancers in an earlier hospital-based case-control study.

Other cancer sites

No significant excess of other tumors has been reported in the largest cohort mortality or incidence studies of production workers. A number of nonsignificantly elevated risks (SMRs or SIRs above 1.0) for deaths or cases of lymphatic and hematopoietic cancers (Morgan *et al.* 1981; Boffetta *et al.* 1997), leukemia (Boffetta *et al.* 1999) and cancers of the urinary bladder (Andersen and Langmark, 1986; Boffetta *et al.* 1997, 1999; Marsh *et al.* 2001a, Stone *et al.* 2004); stomach (Boffetta *et al.* 1997, Gardner *et al.* 1986); intestine (Andersen and Langmark, 1986); rectum (Morgan *et al.* 1981); kidney (Shannon *et al.* 2005); prostate (Morgan *et al.* 1981); bone (Teppo and Kojonen, 1986, Boffetta *et al.* 1997); ill-defined sites (Boffetta *et al*. 1997) and breast, and skin (melanoma)

(Boffetta *et al.* 1999), have been reported in either earlier studies of subcohorts or in the combined follow-up studies.

In population-based, case-control or registry studies of subjects with possible exposure to glass wool, a marginally significant increase in postmenopausal breast cancer and stomach cancer among Finnish women was observed by Weiderpass *et al.* (1999, 2003 respectively) and a marginally significant increase in non-Hodgkin's lymphoma was observed by Hardell and Ericksson (1999). A significant increase in rectal cancer was observed among eight male cases with "substantial" estimated exposure to glass wool in a hypothesis-generating study by Dumas *et al.* (2000). A nonsignificant increase in the risk of ovarian cancer was observed by Vasama-Neuvonen *et al.* (1999) and a nonsignificant increase in colon cancer by Goldberg *et al.* (2001). [The potential contribution of glass fiber exposure to these cancers cannot be distinguished in these studies.]

Studies in Experimental Animals

Numerous studies of various types of commercial insulation glass wools, special-purpose glass fibers, and some experimental fibers have been conducted for carcinogenicity in experimental animals by inhalation, intraperitoneal (i.p.) injection, intrapleural injection, intratracheal instillation, and intrathoracic injection or implantation.

Although all inhalation studies conducted prior to the late 1980s were negative, the results were considered inconclusive because of various study limitations recognized by researchers in the field, including a failure in some studies to produce tumors in positive control groups exposed to asbestos fibers. A series of long-term inhalation studies, which the authors considered to be better designed, were conducted in rats and hamsters in the late 1980s and early 1990s to address the limitations of the earlier studies. Two glass wool fibers (MMVF10 and MMVF11) and two special-purpose fibers (JM100/475 and 104E) were tested in separate studies. Significantly increased incidences of lung carcinomas combined with adenomas occurred in male Wistar rats exposed to 104E microfibers but not to JM100/475 fibers; no significant increases in lung tumors or mesotheliomas were reported for male F344 rats exposed to MMVF10, or MMVF11. In

the most recent inhalation study in male hamsters, mesothelioma was observed in one of 83 animals exposed to JM100/475 glass fibers for 78 weeks.

Significantly increased incidences of peritoneal tumors (primarily mesothelioma) were reported in almost all i.p. injection studies in rats using different type of fibers including insulation fibers such as MMVF10 and MMVF11 and special-purpose fibers such as JM475 (various diameters), M753, and E glass. However, no tumors were observed in some studies testing experimental fibers that have low biodurability. In most cases, tumor incidences were similar to those seen in the asbestos treatment groups. In addition, increased incidences of pleural sarcomas occurred in rats following intrathoracic implantation of some glass fibers (depending on the fiber dimensions) but not others. Increased incidences of neoplasms (mesothelioma, pleural sarcoma, and lung carcinoma) were observed in some intrapleural or intratracheal instillation studies in rats exposed to JM100 or JM104 microfibers and in intratracheal instillation studies in hamsters exposed to JM104 microfibers. No tumors were reported following intrapleural or intratracheal instillation of glass wool in mice, guinea-pigs, or rabbits.

A number of studies, including both intrathoracic implantation and intraperitoneal injection of fibers, have been conducted with the intent of comparing fibers with different characteristics, such as differing fiber dimensions and biopersistence/durability. The earliest of these studies by Stanton and co-workers using intrathoracic implantation of glass fibers and other natural and synthetic fibers led the authors to conclude that fiber dimensions and durability were important in determining the tumorigenicity of the material. Later studies using intraperitoneal injection reached similar conclusions in many cases, but some data suggest that the relationship might not be completely defined by those fiber characteristics.

Deposition, Clearance, and Retention

Fibers that are carried in the inhaled air to the tracheobronchial region are considered *inhalable* while those that reach the alveolar region are considered *respirable*. Fibers that are inhalable but non-respirable can deposit in the extrathoracic and tracheobronchial regions and can cause adverse effects. Deposition refers to the actual dose deposited in

the lung and is influenced by the anatomy and physiology of the airway, respiratory rate, and physical properties of the fiber. Deposition occurs by impaction, sedimentation, interception, and diffusion. Peak deposition occurs in rodents and humans for fibers with aerodynamic diameters of 1 to 2 μm.

Clearance and retention of fibers are affected by chemical composition, size distribution, number of fibers deposited, and time since last exposure. Clearance mechanisms also depend on the region of deposition. Short fibers are readily phagocytized by alveolar macrophages and transported from the lower lung to the upper airways and cleared through the mucociliary escalator. Long fibers are resistant to phagocytosis, but depending on the fiber type, may be subject to dissolution and transverse breakage. Particle overload (which has been observed in rats) occurs when the deposition rate of poorly-soluble, low cytotoxic particles exceeds the normal clearance rate, and can result in adverse effects.

Biodurability and Biopersistence

Biodurability describes the rate of removal through dissolution or disintegration; biopersistence includes biodurability plus physiological clearance and refers to the capacity of a fiber to persist and to conserve its chemical and physical features over time in the lung. Biodurability is expected to be similar in rats and humans, but biopersistence may be substantially different due to differences in the physiological clearance mechanisms. In general, biodurability of various fibers in the lung has been ranked as follows: glass fibers < refractory ceramic fibers < chrysotile asbestos < amphibole asbestos. Highly durable fibers, such as asbestos, are resistant to dissolution and transverse breakage. Although experimental dissolution rates for glass fibers show variability (up to a 30-fold range), they generally show some correlation with clearance rates of long fibers in short-term biopersistence studies. Certain components of SVFs are subject to leaching resulting in changes in composition over time. The fibers become weaker from fractures, peeling, and pitting and may break.

Toxicity

Several studies have evaluated mortality from non-malignant respiratory disease or morbidity related to the respiratory system among workers exposed to glass wool. A significantly elevated SMR for non-malignant respiratory disease was found in the earlier updates, but not the most recent update of the large U.S. cohort study. Mixed findings have also been observed for adverse respiratory symptoms, pulmonary function, and lung abnormalities (detected on chest radiographs); workers in some studies were also exposed to asbestos.

Various types of glass wool fibers (MMVF10, MMVF11, 104E glass fibers, JM100/475 microfibers) caused adverse lung effects (such as inflammation and fibrosis) in rats exposed by inhalation (Hesterberg *et al.* 1993, 2002, Cullen *et al.* 1990, Bellmann e*t al.* 2003, Bermudez *et al.* 2003). In hamsters, inhalation of MMVF10 fibers caused inflammatory effects, but not fibrosis (Hesterberg *et al.* 1993, Bermudez *et al.* 2003). In cytotoxicity studies, longer fibers induced greater toxicity in rat alveolar macrophages (Blake *et al. 1*998, Hurst *et al.* 1994).

Genetic and Oxidative Damage

Glass fibers were shown to induce production of reactive oxygen species in cell-free systems and cultured cells, to damage DNA, and to cause chromosomal aberrations, nuclear abnormalities, mutations, gene amplification in proto-oncogenes, and cell transformation in mammalian cells. However, glass wool fibers did not cause mutations in bacteria or cause sister chromatid exchange in mammalian cells, but only two types of fibers were tested in each of these assays. Glass wool fibers also induced DNA strand breaks (measured by the comet assay) in macrophages and lung epithelial cells, and oxidative stress in rats, but did not induce mutations *in vivo*. Further, fiber persistence may also lead to inflammation-driven (indirect) genotoxicity, as reactive inflammatory cells release reactive oxygen species, growth factors, and cytokines. Fiber characteristics did not appear to be important in the production of reactive oxygen species, and studies assessing oxidative damage by different endpoints were positive for both special-purpose fibers and insulation glass wool fibers. Similarly, fibers of different lengths and diameters

were able to cause DNA damage in mammalian cells. However, effects on chromosomes and nuclear abnormalities may be related to fiber characteristics; longer fibers appeared to be more potent in causing these genotoxic effects. Some studies suggested that thinner fibers were also more effective. Results from cell transformation studies also suggested that longer and thinner fibers produced higher transformation efficiency.

Mechanistic Data

Several investigators have evaluated fiber characteristics (dimensions and durability or biopersistence) and tumorigenicity in studies in experimental animals. These studies (by intraperitoneal injection and intrathoracic implantation) show that fiber dimensions and durability were important determinants of tumorigenicity. In intrathoracic implantation studies, pleural sarcomas were correlated with fiber dimensions; long thin fibers were associated with the highest tumor incidence. Fibers with a high dissolution rate tended to have a low potency in the intraperitoneal assay. A relationship between biopersistence in the lung and pathology was also observed in inhalation studies in rats. Clearance half-times of long fibers (> 20 μm) were approximately 400 to 800 days for two types of asbestos, 80 days for E glass, 50 days for JM100/475 glass, 15 days for MMVF10, and 9 days for MMVF11.

The major proposed mechanisms of fiber-induced carcinogenicity are related to the physical and chemical properties (such as size or dimensions, durability, surface reactivity, and chemical composition) of the fibers and to the inflammatory response that results from the inhalation of fibers. Fiber size affects deposition and clearance, and biodurabilty and biospersistence are related to biological effects. Fibers can directly interact with target cells (epithelial cells, mesothelial cells, fibroblasts) leading to an inflammatory response and/or genotoxicity. Fibers may induce genotoxic effects by interacting with the spindle apparatus of chromosomes, directly damaging DNA or indirectly damaging DNA through chronic inflammation. Alveolar macrophages are activated in response to particulates or fibers deposited in the lung, resulting in increased release of reactive oxygen species, chemical mediators, and cytokines (such as TNF-α) and activation of signalling pathways. A sustained inflammatory reaction may result from

incomplete phagocytosis (frustrated macrophages) and prolonged interaction of persistent fibers with the cell surface. Chronic imbalance between cytokines and growth factors may contribute to tissue injury, proliferation, and/or apoptosis, which may lead to fibrosis and tumors.

Abbreviations

ACGIH: American Conference of Governmental Industrial Hygienists

AES: alkaline earth silicate wools

AGM: absorptive glass mat separator

AIE: average intensity of exposure

AP-1: transcription factor activator protein-1

BGU: β-glucuronidase

BLS: Bureau of Labor Statistics

b.w.: body weight

CHO: Chinese hamster ovary

CI: confidence interval

cm: centimeter

D: diameter

d: day

D_A: aerodynamic diameter

dG: deoxyguanosine

DHHS: Department of Health and Human Services

DNA: deoxyribonucleic acid

EIPPCB: European Integrated Pollution Prevention and Control Bureau

EM: electron microscopy

EPA: United States Environmental Protection Agency

EU: European Union

F: glass filament

F344: Fischer 344 rats

Fpg: formamidopyrimidine DNA glycosylase

FPB: fiber production group

F.R.G.: Federal Republic of Germany

ft: feet

GMIC: Glass Manufacturing Industry Council

GW: glass wool

HAP: hazardous air pollutant

HDN: high alumina containing rock wool

HEPA: high efficiency particulate air [filter]

h: hour

HSPP: Health and Safety Partnership Program

HT: high-alumina, low-silica wools

i.p.: intraperitoneal

i.pl.: intrapleural injection

i.t.: intratracheal instillation

i.th.: intrathoracic implantation

IARC: International Agency for Research on Cancer

ICD: International Classification of Diseases

IFN: interferon

IGW: insulation glass wool

IL: interleukin

JM: Johns Manville

K: kurz, German for short

K_{diss}: dissolution rate

KI: carcinogenicity index

KNB: soluble components index

L: length (lange, German for long)

LDH: lactate dehydrogenase

LM: light microscopy

M: medium

m: meter

MFTD: maximum functionally tolerated dose

mg: milligram

MMMF: man-made (or machine-made) mineral fiber

MMVF: man-made (or machine-made) vitreous fibers

MMWR: Morbidity and Mortality Weekly Report

MN: Manville

MTD: maximum tolerated dose

NA: not applicable

NAICS: North American Industrial Classification System

NAIMA: North American Insulation Manufacturers Association

NF: nuclear transcription factor

NF-κB: nuclear factor kappa B

NHL: non-Hodgkin's lymphoma

NIOSH: National Institute for Occupational Safety and Health

NMRD: non-malignant respiratory disease

NR: not reported

NS: not specified

NTP: National Toxicology Program

8-OHdG: 8-hydroxy-2'-deoxyguanosine

OR: odds ratio

OSHA: Occupational Safety and Health Administration

p: density

PEL: permissible exposure limit

PVNO: polyvinyl-pyridine-N-oxide

r: correlation coefficient

R^2: coefficient of determination, a statistical measure of goodness of fit of a model

RCF: refractory ceramic fiber

Rfib: respirable fibers

Rfib no FOR: respirable fibers exposure without concurrent formaldehyde exposure

Rfib + FOR: concurrent respirable fibers and formaldehyde exposure

RoC: Report on Carcinogens

ROS: reactive oxygen species

RR: relative risk

RSC: respiratory system cancer

S&S: Schleicher & Schuell

SEM-EDX: scanning electron microscopy with energy-dispersive X-ray microanalysis

SES: socio-economic status

SIR: standardized incidence ratio

SMR: standardized mortality ratio

SPF: special-purpose glass fibers

SVFs: synthetic vitreous fibers

$T_{1/2}$: half-time

TIMA: Thermal Insulation Manufacturers Association

TLV: threshold limit value

TNF: tumor necrosis factor

TRGS: Technical Rules for Hazardous Substances (Germany)

TWA: time-weighted average

U.K.: United Kingdom

UICC: Union Internationale Contre le Cancer (International Union Against Cancer)

USCB: United States Census Bureau

USDOL: United States Department of Labor

USITC: United States International Trade Commission

WHO: World Health Organization

wk: week

$WT_{1/2}$: weighted lung clearance half-time

WTC: World Trade Center

χ^2: chi-square statistical test

yr: year

μm: micron, micrometer, one-millionth of a meter

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1 Introduction

Glass wool refers to fine glass fibers forming a mass resembling wool and most commonly used for insulation and filtration. Glass is an amorphous material produced by solidification from a molten state without crystallization and containing a glass former (*e.g.*, silicon dioxide [SiO_2], boron trioxide [B_2O_3] phosphorus pentoxide [P_2O_5], or germanium dioxide [GeO_2]) that can be melted and quenched into a glassy state (IARC 2002). Silicon dioxide is the major glass former used for commercial applications because of its availability and low cost, but commercial glasses generally include additional oxides that modify the physical and chemical properties of the glass product, including viscosity, which is an important characteristic for fiberization. These modifiers include oxides of aluminum, titanium, zinc, magnesium, lithium, barium, calcium, sodium, and potassium.

There are two categories of glass wool based upon usage in commercial applications: insulation glass wool and special-purpose fibers. Insulation glass wools are used for applications such as thermal, electrical, and acoustical insulation and in weatherproofing, while the term "special-purpose glass fibers" is used to describe a category of fibers distinguished by their use in specialized products that include aircraft and aerospace insulation, battery separators, and high-efficiency filters.

Glass wool (respirable size) has been listed in the *Report on Carcinogens* since the Seventh Edition (1994) as *reasonably anticipated to be a human carcinogen*. It was nominated for delisting from the Report on Carcinogens by the North American Insulation Manufacturers Association based on the 2002 IARC reevaluation of glass wool. The 2002 IARC monograph evaluated Man-Made Vitreous Fibers, which included glass wool, as well as continuous glass filament, rock (stone) wool, slag wool, refractory ceramic fibers, and newly developed fibers. Glass wool was further divided in the categories of insulation glass wool and special-purpose fibers (See Sections 1.1.2 and 1.2). The 2002 IARC Working Group concluded that there was *inadequate evidence* in humans for the carcinogenicity of glass wool. They further concluded that there was *limited evidence* in experimental animals for the carcinogenicity of insulation glass wool

and classified insulation glass wool as Group 3, *not classifiable as to its carcinogenicity in humans.* Special-purpose glass fibers such as E-glass and 475 fibers were classified as Group 2B, *possibly carcinogenic to humans,* based on *sufficient evidence* in experimental animals.

The RoC draft background document reviews the literature on glass wool fibers. There are considerable differences in the chemical compositions and physical characteristics of glass fibers, which may influence the toxicity and potential carcinogenicity of the fibers. The expert panel will be asked to review glass wool fibers and make a recommendation on the listing status of glass wool fibers or categories of glass wool fibers for the 12th RoC.

The following sections provide an overview of the various categories of synthetic vitreous fibers (SVFs) (Section 1.1), the chemical and physical characteristics of glass wools (Section 1.2), and methods for fiber classification (Section 1.3).

1.1 Synthetic vitreous fibers

SVFs are a large category that comprises glass wools, as well as other types of glass fibers not covered by this nomination, e.g., continuous glass filaments, and other types of "wools" such as rock wool, slag wool, and ceramic fibers. The general class of SVFs is defined in Section 1.1.1, and the categories of SVFs as defined by IARC (2002) are discussed in Section 1.1.2.

1.1.1 Definition of SVFs

SVFs are manufactured inorganic fibrous materials that contain aluminum or calcium silicates, and are made from a variety of materials, including rock, clay, slag, or glass (ATSDR 2004). Fibers are distinguished from other irregularly shaped particulate matter based on their tendency to form particles with a large aspect ratio (length to diameter ratio). Fibrous particulate matter can be either naturally occurring, like asbestos, or synthetic. SVFs differ from asbestos and other naturally occurring mineral fibers because they have an amorphous or glass-like rather than a crystalline structure. The absence of a crystalline structure can be used to aid in their identification. Historically SVFs have been referred to as man-made mineral fibers (MMMFs), or man-made vitreous fibers

(MMVFs), although the terms used in the United Kingdom have been defined as "machine-made" to preserve the acronyms and maintain gender neutrality. The exact nomenclature and taxonomy used to classify these materials have changed over time and are currently the focus of debate as reviewed by Moore *et al.* (2002).

Glass wool fibers were first introduced into commerce in the 1930s and are now among the world's most extensively used insulating materials. IARC (2002) described wool (such as glass wool) as "a mass of tangled, discontinuous fibres of variable lengths and diameters" and contrasted it with filaments, "which are continuous fibres (of indeterminate length) with diameters having ranges that are more uniform and typically thicker than those of wool."

1.1.2 Categories of SVFs

SVFs and other mineral fibers have been classified according to origin (natural versus manufactured), chemistry (organic and inorganic), physical form and morphology (e.g., filaments and wools), or commercial applications (e.g., insulation wools and special-purpose fibers). IARC (2002) divided SVFs into the categories shown in Figure 1-1. However, there are a number of commercial and experimental products within each category that vary in composition, dimensions, durability, and biological activity. The categories identified by IARC are based on physical form and commercial applications, but Moore *et al.* (2002) and other authors have proposed methods for grouping fibers according to potential biological activity (Figure 1-2).

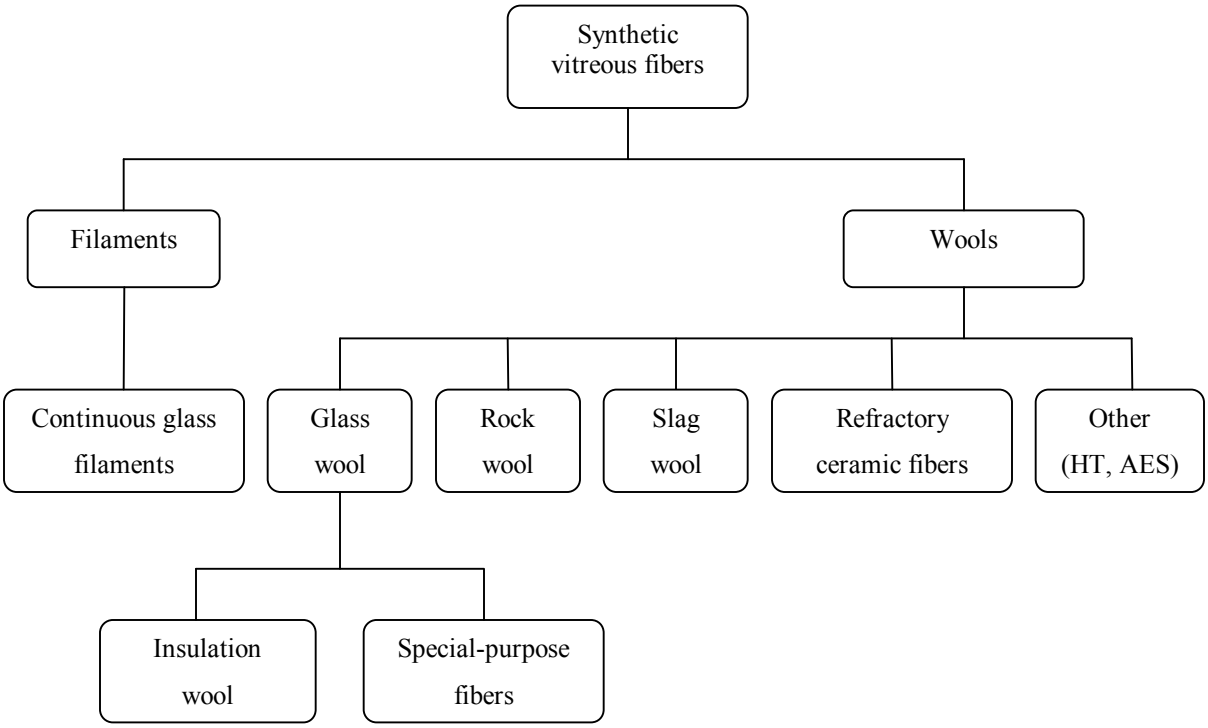

Figure 1-1. Categories of synthetic vitreous fibers (from IARC 2002)
HT = high-alumina, low-silica wools; AES = alkaline earth silicate wools

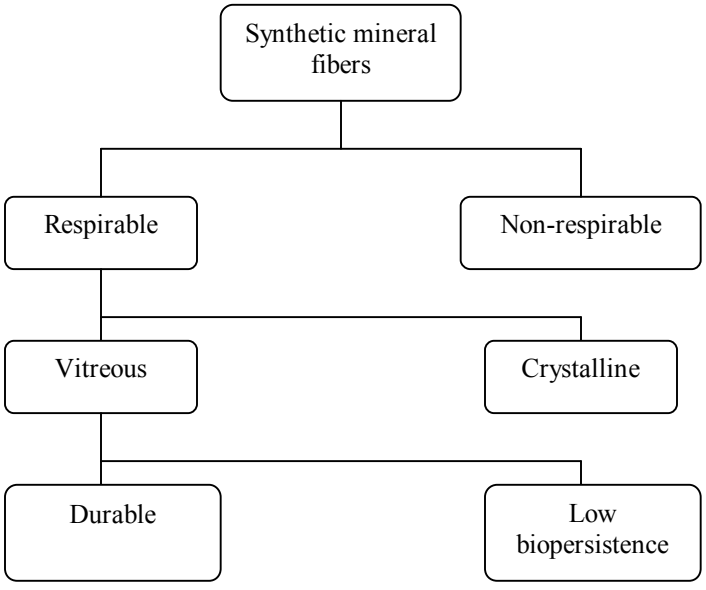

Figure 1-2. Proposed fiber categorization scheme to facilitate hazard identification (adapted from Moore *et al.* 2002)

As illustrated in Figure 1-1, glass wool can be divided into two sub-categories, insulation wool and special-purpose fibers. Special-purpose fibers make up a small fraction of the glass wool market and are used, as the name implies, in specialized applications (see Section 2.1). Special-purpose fibers are more highly engineered than glass wool and typically contain oxides such as ZnO, ZrO_2, and BaO that improve the ability to fiberize the glass at diameters below 1 μm and increase durability (Carey 2004). Therefore, special-purpose fibers typically are smaller in diameter, more durable, and more biopersistent than the typical insulation glass wool. Biopersistence and toxicity will be discussed later in this review. Although most published information about special-purpose fibers refers to 475 and E-glass, there are many other types. Although each manufacturer has its own product designations, special-purpose fibers share in common certain physical and chemical characteristics described in this section. In addition to 475 and E-glass, examples of other special-purpose fibers include UPF 363, Evanite M and B (a version of 475 glass), and Lauscha A-, B- (also a version of 475 glass), and C-glass. Table 1-1 lists examples of insulation glass wools, and Table 1-2 lists examples of special-purpose glass fibers used in the studies reviewed in this document.

Table 1-1. Examples of commercial and experimental insulation glass wools

Fiber description	Examples	Comments
Insulation glass wools	French glass fibers (Saint Gobain), Owens-Corning general building insulation, Manville 901 building insulation, CertainTeed B glass, Insulsafe II	Commercial products
Respirable fractions derived from commercial insulation wools	MMVF10, MMVF10a MMVF11	Derived from Manville 901 Derived from CertainTeed B
Experimental fibers	B, M, P, and V fibers B-01-0.9, B-09-0.6, B-09-2.0	European experimental fibers, not commercially produced

Table 1-2. Examples of special-purpose glass fibers

Fiber type	Examples	Comments
475 glass (Tempstran 475)	JM475, JM100/475, JM100, JM102, JM104, JM108, JM110, JM112, Code[a] 100 or Manville Code 100, MMVF33	475 glass is manufactured in different diameters expressed as Codes. JM100, JM102, JM104, etc. reflect the relative diameter with the smaller number representing a finer diameter (see Table 1-3).
E-glass	104E, JM104E, MMVF32	E-glass is a calcium aluminum borosilicate glass with a much higher calcium and aluminum content and a lower silica component than is typical for insulation wools.
Experimental fibers	Bayer B1, B2, B3	Not commercialized
Other	JM753 Owens-Corning AAA-10 microfiber S&S 106	Discontinued product Special-purpose fiber from a manufacturer other than Johns Manville

[a]The code refers to the diameter of the fiber.

Table 1-3. Codes for Manville glass fibers

Designation	Range of nominal diameters (μm) [a]	Glass type[b]
JM80	0.24–0.28	475
JM100	0.28–0.38[c]	475
JM102	0.35–0.42[c]	475
JM104	0.43–0.53	475, E
JM106	0.54–0.68	475, E
JM110	1.9–3.0	475

Source: WHO 1988.
[a]WHO (1988) noted that these specifications were current at the time of that publication; however, specifications have changed over time.
[b]475 = general purpose borosilicate; E = electrical grade, alkali-free borosilicate [WHO definitions].
[c][No explanation was reported by WHO for the overlap in range of diameters for codes JM100 and JM102.]

1.2 Chemical and physical properties

The chemical composition of glass wool products varies depending on the manufacturing requirement and end-use, but almost all contain silicon dioxide as the single largest oxide ingredient (IARC 2002). Silicon dioxide or one of a few other oxides is required in order to form glass, and these oxides are known as "glass formers." The essential property of a glass former is that it can be melted and quenched into the glassy state. Other oxides are added as stabilizers and modifiers or fluxes. In addition, various lubricants, binders,

antistatic agents, extenders and stabilizers, and antimicrobial agents may be added to various products. Lubricants may be added to reduce dust generation. Binders, such as phenol-formaldehyde resins, melamine, or acrylic resins, may serve to hold the fibers together. The binder content for most insulation wool products is low but may reach 25% for some products.

Table 1-4 provides chemical composition data that were identified for various glass fibers discussed in this document.

Table 1-4. Reported chemical compositions for various glass fibers (expressed as oxide mass percentages)

Fiber	SiO_2	Al_2O_3	B_2O_3	CaO	MgO	BaO	ZnO	ZrO_2	TiO_2	Na_2O+K_2O	Na_2O	K_2O	$FeO+Fe_2O_3$	Fe_2O_3	P_2O_5	MnO	SO_3	F_2
MMVF10[a]	57.4	5.17	8.53	7.65	4.16	-	-	-	0.03	-	15.5	1.07	-	0.07	-	-	0.07	-
MMVF10a[b]	57.2	5.1	8.4	7.17	4.48	0.01	-	0.02	< 0.01	-	15.6	1.04	-	0.05	-	-	< 0.03	-
MMVF11[a]	63.5	3.76	4.36	7.27	2.77	-	-	0.02	0.06	-	15.71	1.38	-	0.27	-	-	0.21	-
B[c]	61.4	0.46	3.4	16.3	2.9	-	-	-	0.02	-	14.9	0.32	-	0.06	-	-	-	-
M[c]	57.4	0.5	12	8.3	3.5	-	-	-	-	-	17.9	0.34	-	0.05	-	-	-	-
P[c]	50.93	2.5	-	30.9	10.2	-	-	-	0.09	-	3.55	0.8	-	0.95	0.03	0.05	-	-
V[c]	63.3	2.07	8.2	7.05	3.16	-	-	-	-	-	15	1.15	-	0.12	-	-	-	-
Bayer B-1, B-2[d]	60.7	-	3.3	16.5	3.2	-	-	-	-	-	15.4	0.7	0.2	-	-	-	-	-
Bayer B3[d]	58.5	5.8	11	3	-	5	3.9	-	-	-	9.8	2.9	0.1	-	-	-	-	-
Bayer B9[e]	62	-	5	8.8	-	-	-	-	6	-	15	2.9	-	-	-	-	-	-
E-glass microfiber[f]	54.3	13.9	7.6	19.5	2.4	-	-	-	0.7	-	0.8	0.1	-	0.2	-	-	-	-
JM100/475[g]	74.5	1.9	-	6.8	-	6.9	-	-	-	-	0.8	8.4	0.6	-	-	-	-	-
JM104E[g]	59.7	11.7	-	28	0.5	-	-	-	-	-	-	-	-	-	-	-	-	-
JM475[d]	57.9	5.8	10.7	-	-	5	-	-	-	-	10.1	2.9	0.1	-	-	-	-	-
JM753[d]	63.4	-	5.6	6.1	3	-	-	-	-	-	14.6	1.1	2	-	-	-	-	-
MMVF32[h]	54.3	13.9	7.59	19.52	2.43	0.2	-	-	0.66	-	-	-	-	-	-	-	-	-
MMVF33[i]	58.4	6	11	1.8	-	4.9	4.9	-	-	12.6	-	-	-	-	-	-	-	-
UPF 363[j]	58–59	5	7–8	0–0.2	<0.1	-	-	4	8	16–18	-	-	-	-	-	-	-	<2
Evanite, M[j]	65.8–71.2	3.3–4.4	4.2–5.3	4.8–6.6	2.3–3.3	0–0.2	0.0.4	-	-	-	10.9–12.9	1.6–2	-	-	-	-	-	0.5–1

Fiber	SiO_2	Al_2O_3	B_2O_3	CaO	MgO	BaO	ZnO	ZrO_2	TiO_2	Na_2O +K_2O	Na_2O	K_2O	FeO+ Fe_2O_3	Fe_2O_3	P_2O_5	MnO	SO_3	F_2
Evanite B[j]	56.4–60.4	5.2–6.4	10–12	1.5–2.3	0.15–0.5	4.5–5.5	3.5–4.5	-	-	-	9–11	2.6–3.4	-	-	-	-	-	0.3–0.7
Lauscha glass A[j]	69–72	2.5–4	<0.1	5–7	2–4	-	0–2	-	-	-	10.5–12	4.5–6	-	-	-	-	-	-
Lauscha glass B[j]	55–60	4–7	8–11	1.5–5	0.7–2	3.6–6	2–5	-	-	-	9.8–13.5	2.5–4	-	-	-	-	-	<1
Lauscha glass C[j]	63–67	3–5	4–7	4–7	2–4	<0.1	<0.1	-	-	-	14–17	0–2	-	-	-	-	-	<1
JM104/475[f]	57.9	5.8	10.7	3.0*	*	5.0	3.9	-	-	-	10.1	2.9	-	0.1	-	-	-	-
Glass wool[f]	64.9	3.1	4.7	7.0	2.9	0.1	-	-	0.1	-	15.3	1.5	-	0.3	-	-	-	-
CertainTeed B[k] glass	63.4	3.88	4.45	7.45	2.82	-	-	0.0	0.06	-	15.45	1.32	-	0.25	0.0	0.01	0.33	-
CM 44[k]	61.7	0.97	9.2	7.15	2.94	-	-	0.0	0.02	-	16.06	0.59	-	0.11	1.05	0.01	0.2	-
B-01/09[k]	61.5	0.31	3.15	15.6	2.99	-	-	0.04	0.02	-	15.51	0.72	-	0.11	0.0	0.01	0.0	-
B-01[l]	62.0	-	5.0	8.8	-	-	-	-	6.0	-	15.0	2.9	-	-	-	-	-	-

[a] Hesterberg *et al.* 1993
[b] McConnell *et al.* 1999
[c] Insulation wools developed to be more biosoluble (Grimm *et al.* 2002)
[d] Pott *et al.* 1991
[e] Roller *et al.* 1996
[f] Bellmann *et al.* 2003
[g] Cullen *et al.* 2000
[h] Hesterberg *et al.* 1998
[i] Moore *et al.* 2002
[j] Carey 2004
[k] Bernstein *et al.* 1996
[l] Roller *et al.* 1996
* Bellman *et al.* footnote for CaO states "Include MgO."

Important physical properties include fiber dimensions, density, and durability. Glass wool fiber diameters vary within a product but follow an approximately log-normal distribution. However, the fiber diameter is not an inherent property of the type of fiber but is controlled by the manufacturing process. All SVFs are manufactured to nominal diameters that vary based on the manufacturing process and the fibers' intended use (ACGIH 2001). The nominal diameter is an estimate of the average fiber diameter of the product. ACGIH (2001) reported that insulation wool products typically have nominal diameters of 1 to 10 μm, although it was noted that most products have a nominal diameter within the 3 to 10 μm range. Special-purpose fibers have nominal diameters that range typically from 0.1 to 3 μm. Current glass wool production processes are not capable of producing fibers only at the nominal diameter, and as a result, the diameters of individual fibers in a glass wool product vary widely around the nominal diameter. IARC (2002) noted that a product with an average diameter of 5 μm will contain fiber diameters ranging from < 1 to > 20 μm (IARC 2002). Unlike crystalline fibers, such as asbestos, glass fibers do not split lengthwise into fibers with smaller diameters. They can only break across the fiber resulting in shorter fibers with the same diameter.

The manufacturing process also affects fiber length. In glass wool insulation, most fibers are several centimeters long; however, fibers with lengths of less than 250 μm (considered by IARC as the upper limit of respirability) probably are present in all glass wool products (IARC 2002). Mean fiber lengths for JM475 are 1 to 1.5 mm and for Evanite filter grade special-purpose fibers they are ≥ 4.5 mm (Carey 2004). Fiber densities are not as variable as diameter and length and are typically 2.4 to 2.6 g/cm^3 (IARC 2002).

1.3 Fiber classification

Fibers, classified by their physical dimensions, have been basically defined since the late 1950s as being greater than five μm long and having a length-to-width aspect ratio of at least 3:1 (i.e., the fiber is at least three times longer than its width) (Breysse *et al.* 1999, Walton 1982). Other more recent definitions have suggested that an aspect ratio of 5:1 will more readily discriminate fibrous from irregularly shaped particles. The World Health Organization (WHO) defines fibers as being greater than 5 μm long, thinner than

3 μm, and having an aspect ratio of > 3:1. The United States National Institute for Occupational Safety and Health (NIOSH) has two sets of fiber definitions, the so called "A" and "B" rules (NIOSH 1994). Table 1-5 compares the NIOSH and WHO fiber definitions.

Depending on the production process, fibers can have relatively large or small diameters. The diameter of a fiber is an important property because very thin fibers can enter the respiratory tract and deposit deep in the lungs (see Section 2). Fibers with diameters less than 3 μm are usually considered able to penetrate into the lower respiratory tract of humans. These fibers are usually called "respirable" although the term thoracic is more accurate. Baron has shown that the fraction with diameter less than 3 μm agrees well with the thoracic deposition fraction (Baron 1996). Since possible bronchogenic effects (i.e., lung cancer) are under consideration, a thoracic fraction is appropriate. This review will focus on the so-called "respirable" glass wool fibers since these are the fiber sizes that present the greatest inhalation risk.

Table 1-5. Comparison of WHO and NIOSH fiber counting definitions

Source	Aspect ratio	Length, (μm)	Diameter, (μm)
NIOSH 7400 Method "A" Rules	≥ 3:1	> 5	NS
NIOSH 7400 Method "B" Rules	≥ 5:1	> 5	< 3
WHO European Reference Method	≥ 3:1	≥ 5	< 3

NS = not specified.

Fibers have also been examined based upon other characteristics, including biopersistence, retention and clearance rates, and biodurability. Dose, dimension, and durability have been termed the three Ds, all of which are important in determining the carcinogenicity of fibers (see Section 5.3). Several classification systems exist based on these characteristics; the following is a discussion of the European and German classification systems for labeling SVFs.

1.3.1 European classification system

In 1997, the European Union (EU) established criteria for labeling and classifying SVFs based on their potential human health hazard under the Dangerous Substances Directive

[67/548/EEC] (Hesterberg and Hart 2001). Under this system, all SVFs are considered irritants and are classified for carcinogenicity according to the criteria in Table 1-6.

Table 1-6. European carcinogenicity classification

Classification	Definition & Criteria
(1) Carcinogen	Substances known to be carcinogenic to man. There is sufficient evidence to establish a causal association between human exposure to the substance and the development of cancer.
(2) Probable Carcinogen	A substance that should be regarded as if it is carcinogenic to man. There is sufficient evidence to provide a strong presumption that human exposure to the substance may result in the development of cancer, generally on the basis of appropriate long-term animal studies or other relevant information. SVF Criteria[a]: Diameter ≤ 6 μm [b]; Solubility Index (KNB) ≤ 18%
(3) Possible Carcinogen	A substance that is of concern as a possible human carcinogen, but available information is not adequate for a valid assessment. There is some evidence from appropriate animal studies, but this is insufficient to place the substance in Category 2. SVF Criteria[a]: Diameter ≤ 6 μm [b]; Solubility Index > 18%.
(0) Not classified as a Carcinogen	Exempt from carcinogenicity classification (but still considered an irritant). SVF Criteria[a]: Diameter > 6 μm [b]

Source: Hesterberg and Hart 2001.
[a] Criteria used to classify insulation wools composed of fiber glass or rock/stone/slag wools that have not been evaluated in a carcinogenicity or biopersistence test.
[b] Nota R of Commission Directive 97/548/EEC, 12/5/97, states: "length-weighted geometric mean diameter less 2 standard errors greater than 6 μm." This is roughly equivalent to a geometric mean diameter of 6 μm.

Based on this classification system, SVFs with diameters greater than 6 μm are not considered carcinogenic (because they are nonrespirable), but they are considered irritants (Hesterberg and Hart 2001). Untested SVFs with diameters ≤ 6 μm are categorized in Category 2 or 3 depending on the results of the Soluble Components Index (KNB). The KNB is equal to the sum of the percent composition of the more rapidly dissolving components ($Na_2O + K_2O + CaO + MgO + BaO$). This sum of alkali and alkaline earth oxides is also described by the term "Z-score," and fibers with a Z score less than or equal to 18% are considered to represent a greater potential hazard than those with a Z score greater than 18% (Moore *et al.* 2002). However, Moore *et al.* (2002) noted that fibers are not customarily defined by their total alkali and alkaline earth oxides, and that it is not clear that such a "bright line" can divide the continuum of glass fibers into categories of risk or hazard. Nevertheless, Moore noted that the EC Directive would place glass microfibers (i.e., special-purpose fibers) in Category 2 (probable), and

standard insulation glass wools in Category 3 (possible). [However, many of the special-purpose fibers have Z scores > 18%, e.g., JM104E = 28.5 and M753 = 24.8, and thus would be included in Category 3 along with insulation glass wools.] A Category 3 fiber can be exempted from carcinogenicity classification (but still considered an irritant) if it passes one of the four tests described in Table 1-7. All of these tests are conducted in rats. In their final conclusions, Moore *et al.* reported that they did "not believe that there is scientific justification for the use of Z scores as a basis for classifying substances as carcinogens."

Table 1-7. European tests for upgrading the classification of an SVF

Test	Criterion for Passing Test
Intraperitoneal injection test	Noncarcinogenic
Chronic inhalation test	Noncarcinogenic
Inhalation biopersistence test	Fibers longer than 20 μm: $WT_{1/2}$[a] < 10 days
Intratracheal instillation biopersistence test	Fibers longer than 20 μm: $WT_{1/2}$ < 40 days

Source: Hesterberg and Hart 2001.
[a] $WT_{1/2}$ = weighted lung clearance half-time.

The weighted lung clearance half-time ($WT_{1/2}$) is calculated by weighting each clearance half-time ($T_{1/2}$) by multiplying it by the proportion of fibers in that pool ($a_1/[a_1 + a_2]$ or $a_2/[a_1 + a_2]$ and then summing the two weighted $T_{1/2}$ values and dividing by 2 (Hesterberg and Hart 2001).

1.3.2 German classification system

Soon after the European classification system was enacted, Germany enacted its own criteria for classifying SVFs according to carcinogenicity (Hesterberg and Hart 2001). Germany considers every SVF to be carcinogenic, and very strict worker protection requirements are required unless the fibers pass one of the three tests outlined in Table 1-8. These include the carcinogenicity index (KI), biopersistence test, and intraperitoneal (i.p.) injection test. The KI is another solubility index that tries to predict fiber dissolution rate based on fiber composition. In the biopersistence test (intratracheal instillation), rats are instilled with 0.5 mg of fibers per day for 4 days, with a total dose of 2 mg. Lung burdens are evaluated for up to 3 months. The lung clearance half-time ($T_{1/2}$) for the fibers must be less than 40 days to pass this test. The intraperitoneal injection test is

conducted using the same protocol as that used by the European carcinogenicity classification (see Section 1.3.1) (Bernstein and Sintes 1999). In order to pass this test, the tumor incidence must not be significantly elevated above the level seen in controls (Hesterberg and Hart 2001).

Table 1-8. German tests for noncarcinogenic classification

Test	Criterion for Passing Test
KI (carcinogenicity index)	KI > 40 KI = $[Na_2O + K_2O + CaO + MgO + BaO + B_2O_3]^a - 2 \times (Al_2O_3)]^a$
Biopersistence test: intratracheal instillation	$T_{1/2}$ of WHO fibers < 40 days
Intraperitoneal injection test	noncarcinogenic

Source: Hesterberg and Hart 2001.
[a] Concentrations of oxides as per cent of total mass.

1.4 Summary

Glass is an amorphous material produced by solidification from a molten state without crystallization and containing a glass former that can be melted and quenched into a glassy state. Silicon dioxide is the major glass former used for commercial applications. Glass wool refers to fine glass fibers forming a mass resembling wool and most commonly used for insulation and filtration. Glass wool fibers were first introduced into commerce in the 1930s and are now among the world's most extensively used insulating materials. Special-purpose fibers make up a small fraction of the SVF market and are used, as the name implies, in specialized applications.

Glass wool fiber diameters vary within a product but follow an approximately log-normal distribution. The fiber diameter is controlled by the manufacturing process. Fiber diameters vary based on the manufacturing process and the fibers intended use. The nominal diameter is an estimate of the average fiber diameter of the product. Insulation wool products typically have nominal diameters of 1 to 10 μm and special purpose fibers have nominal diameters of 0.1 to 3 μm. The diameters of individual fibers in a glass wool product vary widely around the nominal diameter. Unlike crystalline fibers, such as asbestos, glass fibers do not split lengthwise into fibers with smaller diameters, but only break across the fiber resulting in shorter fibers with the same diameter.

SVFs and other mineral fibers have been classified according to origin (natural versus manufactured), chemistry (organic and inorganic), physical form and morphology (e.g., filaments and wools), or commercial applications (e.g., insulation wools and special-purpose fibers).

Fibers, classified by their physical dimensions, have been basically defined since the late 1950s as being greater than five μm long and having a length-to-width (aspect) ratio of at least 3:1 (i.e., the fiber is at least three times longer than its width). WHO defines fibers as being greater than 5 μm long, thinner than 3 μm, and having an aspect ratio of > 3:1.

Fibers have also been examined based upon other characteristics, including biopersistence, retention and clearance rates, and biodurability. The European Union (EU) and Germany have established criteria for labeling and classifying SVFs based on their potential human health hazard.

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2 Human Exposure

The vast majority of glass wool manufactured in the United States is used in home and building insulation products. A small percentage is used for a number of special applications; such as for aircraft and aerospace insulation, as battery separators, and in filtration products. Occupational exposure can occur in glass wool production facilities and other facilities, such as fiberglass insulating operations and pipe insulation installation. Limited information is available on environmental exposure and occurrence of glass fibers, but general population exposure can occur where they are used, e.g., as insulation materials, or from fibers in the air near manufacturing facilities.

This section provides information on the uses of glass fibers and glass fiber products (Section 2.1); on the manufacturing process, production levels, and levels of imports and exports (Section 2.2); on occupational exposures (Section 2.3); on environmental occurrence and general population exposure (Section 2.4); on biological indices of exposure (Section 2.5); and on regulations and guidelines for glass fibers that are intended to reduce exposure (Section 2.6).

2.1 Uses for glass fibers

Glass fibers can generally be classified into two categories: low cost general-purpose fibers typically used for insulation applications and premium special-purpose fibers used in limited specialized applications (Wallenberger *et al.* 2001). Another class of glass fibers is the continuous glass filaments, also referred to as glass textile fiber (IARC 2002); however, the filaments are produced in nominal diameters ranging from 5 to 25 μm with very narrow variation around this mean value. Due to the larger diameter of these glass fibers, they are not considered respirable and therefore are not reviewed in this background document.

2.1.1 Glass wool for insulation

Glass wool has many commercially valuable physical properties, including a low thermal conductivity and volumetric heat capacity that enable glass wool materials to be effectively used for insulation purposes. As a result, the primary uses of glass wool are for heat and sound insulation. The largest glass wool use is for home and building

insulation purposes in the form of loose wool, batts (insulation in the form of a blanket, rather than a loose filling), blankets or rolls, or in the form of rigid boards for acoustic insulation. Glass wool is also used for industrial, equipment, and appliance insulation. A summary of the main insulation wool uses is presented in Table 2-1.

Table 2-1. Insulation wool uses

Sectors	Subsectors	Location	Function
Buildings	Residential	Roof, wall, floor	Thermal, acoustic, fire protection
	Offices and shops	Roof, wall, floor	Thermal, acoustic, fire protection
	Schools	Partition Ceiling	Thermal, acoustic, fire protection Acoustic
Transportation	Railway	Partition	Thermal, acoustic, fire protection
	Automotive	Headliner and hood pad	Thermal, acoustic
		Silencer	Acoustic
	Maritime	Partition Fire protection door	Thermal, acoustic, fire protection Fire
	Airplanes	NR	NR
Industry	Buildings	Roof, wall, floor	Thermal, acoustic, fire protection
	Air conditioning	Duct	Thermal
	Fluid transportation	Pipe	Thermal
	Ovens, furnaces	Lining or wall	Thermal
Agriculture	Buildings	Breeding shed	Thermal, fire
Health	Hospitals/medical centers	Roof, floor Partition, wall, door Ceiling	Thermal, acoustic, fire protection Thermal, acoustic, fire protection Acoustic
	Medical equipment	Absorbent pad	NR
Domestic equipment	NA	Oven	Thermal

Source: IARC 2002.
NA = not applicable; NR = not reported.

2.1.2 Non-insulation uses (special-purpose fibers)

Special-purpose glass fibers are limited-production materials compared with insulation glass wool, but they are used for a variety of applications that either require a specialized glass formulation or particular diameter requirements. Typical products have diameters of less than 3 μm and frequently less than 1 μm with an average diameter ranging from 0.1 to 3 μm compared with the average of 1 to 10 μm for insulation glass wool fibers (ACGIH 2001). These specialty fibers are used in aircraft and aerospace insulation, as battery separators, and in filtration products. The largest market for special-purpose glass

fibers is for battery separator media, with the primary component of such media being an acid-resistant borosilicate glass fiber. The purpose of the glass fiber media is to physically separate the positive and negative plates of the battery, while allowing the acid electrolyte to pass through the media (IARC 2002).

Another use of special-purpose glass fibers is in high-efficiency particulate air (HEPA) filters that are used in settings where high-efficiency filtration of air is required. Examples include use in hospitals, clean rooms of pharmaceutical laboratories, nano-technology industries, microbiological laboratories, and nuclear power plants. These filters are used to increase the quality of indoor air, as these filters can remove sub-micron particulate matter (Carey 2004). See Table 2-2 for some examples of special-purpose glass fibers and their commercial uses.

Table 2-2. Some examples of special-purpose glass fibers and their commercial uses

Special Purpose Glass Fiber Use Category	Glass type or trade name	Nominal Fiber Diameter	Composition	End-Use Applications
Battery separator media	LFI C-glass Evanite M-glass JM253 and JM475	0.6–3 μm	acid-resistant borosilicate glass	AGM–absorptive glass mat separator for use in flooded and sealed lead acid batteries automotive, electric vehicle, flashlight, hearing aid, and computer batteries
Filtration: air and liquid	Micro-Strand[a] glass fibers (100 and 200 series)–Johns Manville JM475 Evanite B-glass LFI A- and B-glass	0.2–5.5 μm	varies with product use, but generally high purity fibrous silica	Fiber media containing glass microfibers can be converted into a wide variety of products: batts, blankets, webs, flat or pleated 'papers,' and cylindrical filter cartridges. They can be wrapped, molded, sewn or laminated to other substrates. Final products are used in the nuclear, electronic, automotive, pharmaceutical, aerospace and chemical industries. Corrosion-resistant glass microfibers can be used in clean-room filters for electronics industry applications

Special Purpose Glass Fiber Use Category	Glass type or trade name	Nominal Fiber Diameter	Composition	End-Use Applications
Insulation	Micro-Fiber felt[a] (Johns Manville) JM475	0.6–4 μm	borosilicate glass	Aircraft and spacecraft: thermal and acoustical insulation, gas and air filtration in a medium temperature range (up to 900°F)
	Q-fibers[a] (Johns Manville)	0.75–1.59 μm	High-purity silica (or quartz)	Aerospace, automotive and chemical industry applications (originally developed for manufacturing tile sheathing on space shuttles). Can withstand temperatures up to 2,300°F (1,260° C) Insulation products for nuclear power industry

Source: Zguris *et al.* 2005.
[a]Johns Manville trade names.
LFI–Lauscha Fiber International (A-glass is low boron alkali silicate, B-glass is borosilicate, C-glass is acid resistant borosilicate and E-glass is calcium aluminoborosilicate).

2.2 Production, import, and export information

2.2.1 Production methods

The major methods for fiber manufacture historically have been steam attenuation, the rotary or centrifugal process, and flame attenuation (Dement 1975). Only the latter two methods remain in use today. Glass for fiber manufacture is almost always based on silicon dioxide with varying amounts of other inorganic oxides, including oxides of alkaline earths, alkalis, aluminum, boron, iron, and zirconium (IARC 2002) (see also Table 1-3). In some cases, the additional oxides occur in the raw materials used to make the glass, while in others specific oxides are added in order to enhance the manufacturing process or the performance of the final product. The raw materials commonly used in the manufacture of insulation glass wool and special-purpose fibers are listed in Table 2-3.

Table 2-3. Raw materials commonly used in the manufacture of insulation glass wool and special-purpose fibers

Raw material	Desired element	Source	Insulation glass wool	Special-purpose fibers
Colemanite	B	Mined		x
Dolomite	Ca, Mg	Mined	x	x
Fluorspar	F	Mined		x
Kaolin clay	Al	Mined	x	x
Limestone	Ca	Mined	x	x
Nepheline syenite	Al	Mined	x	
Silica sand	Si	Mined	x	x
Ulexite	B	Mined	x	
Wollastonite	Ca, Si	Mined		x
Zircon sand	Zr, Si	Mined		x
Burned dolomite	Ca, Mg	Processed	x	x
Cullet	Si, Ca, Mg, Na, B	Recycled	x	
Alumina	Al	Manufactured	x	x
Borax (5 H_2O)	B	Manufactured	x	
Magnesite	Mg	Manufactured		x
Manganese dioxide	Oxidizing power	Manufactured	x	
Sodium nitrate	Oxidizing power	Manufactured	x	
Sodium carbonate	Na	Manufactured	x	
Sodium sulfate	Oxidizing power	Manufactured	x	
Zirconia	Zr	Manufactured		x

Source: IARC 2002.

Raw materials for a specific batch of glass fibers are first weighed and blended using automated processes before being added to the fiberglass furnace, where the materials are melted and homogenized at approximately 1,370°C (2,500°F) using either electricity or gas as the heat source (Wallenberger *et al.* 2001).

Rotary or centrifugal method

Steam blowing was initially used in the 1940s but was quickly replaced by the flame attenuation process. Spinning processes were the next innovation to be introduced in the mid-1950s and were further enhanced with the addition of the rotary process, which remains the predominant method of manufacturing today (IARC 2002).

In the rotary process, fibers are produced as centrifugal force extrudes the molten material through small holes in the side of the spinning device (Burgess 1995). In the refiner section of the furnace, the temperature of the glass melt is lowered to about 1,260°C (2,300°F) (IARC 2002). A stream of molten glass from the fiberglass furnace flows along a heated forehearth lined with refractory material to a point directly above the fiber-forming station where it pours through single-orifice bushings into rotary centrifugal spinners (EIPPCB 2001). The molten glass is then extruded from the sidewall holes as small streams of glass to form the primary glass fibers through centrifugal action and aerodynamic drag forces. The primary fibers pass through a circular burner flame, whose hot gases attenuate the fibers to their final diameter and break the fibers into shorter lengths (IARC 2002). The resulting fibers, which have a range of lengths and diameters, form a veil of randomly interlaced fibers, which are sprayed with a phenolic (usually phenol-formaldehyde) resin binder and lubricant (usually mineral oil or paraffin oil) to improve the integrity, resilience, durability, and handling quality of the finished product. The lubricating oils are added to reduce dust and lint formation of the final product and reduce the amount of airborne fibers during their use. A gas-fired oven dries the product and cures the binder. The resin-coated fibers are formed into a mat of fibers. The resultant fibers typically range from 0.5 to 6 μm in diameter; however, the distribution of lengths is extremely broad (Moore *et al.* 2002).

As noted in Section 1, the nominal diameter is an estimate of the average fiber diameter of the wool product; however, within that product, the diameters of individual fibers vary widely around the nominal diameter and all wool products will contain some percentage of respirable fibers (ACGIH 2001). Because smaller fibers become airborne more easily than larger fibers and because larger diameter fibers fall out of suspension in air faster than small diameter fibers, the distribution of airborne fiber diameters will differ from that of the product (ACGIH 2001, Krantz 1988); [i.e., the average diameter of airborne fibers will be smaller than the nominal diameter of the product]. In an assessment of occupational exposures to MMMF in Sweden, Krantz (1988) reported that median diameters of airborne fibers were in all cases much smaller, by almost one order of

magnitude, than the nominal diameters of the products. ACGIH (2001) noted that in general, as nominal diameters decrease, exposure levels increase.

IARC (2002) reported that the mean length of insulation glass wool fibers has been found to range from less than 1 cm to several cm in length; although fibers with lengths of less than 250 μm (which IARC reported as the upper limit for respirability) probably are present in all wool products. Fiber length contributes significantly to the ease with which a fiber becomes airborne, with shorter fibers of the same diameter becoming airborne more easily than longer fibers. As noted in Section 1, glass fibers do not break lengthwise, but rather break across the fiber resulting in shorter fibers with the same diameter.

Flame-attenuation method

A flame attenuation process is used to produce very small diameter fibers, and this method is generally used to produce special-purpose fibers. The glass used to produce the fibers can be produced earlier and cooled into preforms, often as glass marbles (EIPPCB 2001). The marbles are added to a heated pot for the production of fibers in a process described as pot and marble.

The flame-attenuation method of producing fibers is a two-step procedure (IARC 2002). In the first step, the melt is drawn through the bushings of the furnace to produce strands of coarse fibers. The fibers are then remelted with a high temperature gas flame, which is usually mounted at right angles to the primary fibers. The flame attenuates the coarse fibers into finer fibers, which are propelled by high-velocity gases through a forming tube. There, the fibers are sprayed with a binder and formed into mats, which can be further processed into a variety of special-purpose applications (IARC 2002). Special-purpose glass fibers are more highly engineered than glass wool products, and thus are significantly more expensive (Carey 2004).

2.2.2 U.S. production

Insulation products comprise the vast majority of SVFs produced in the United States, and glass wool is the predominant SVF used for insulation products. IARC reported that in 1999, North American demand for glass wool insulation made up 54.8% of world

demand in that category, while North American demand for rock or slag wool insulation made up only 7.6% of world demand for that category. In the year 2000, an estimated 3,388 million pounds of fiberglass were used in building insulation (commercial and residential), with approximately 79.1% being produced as batts, blankets, or board, and the remaining 20.9% produced as blown or loose-fill insulation (Maxim *et al.* 2003). Furthermore, Maxim *et al*. presented an estimate that 80.9% of the fiberglass insulation sold was used for residential construction and 19.1% for commercial or industrial construction.

ATSDR (2004) reported 2002 Glass Manufacturing Industry Council (GMIC) data that indicated that 10 major manufacturers were operating about 40 plants within the United States, and the production volume of all glass fiber types, including glass wool, was estimated at about 3 million tons (2.72×10^9 kg) annually.

Special-purpose glass fibers make up a very small amount of the total SVFs produced in the United States, accounting for only about 1% of the total annual production (Carey 2004). In the United States, there are at least four companies that produce special-purpose glass fibers, with imports occurring in increasing amounts from China and other Asian countries. Special-purpose glass fibers products are not generally available to the general public. They usually are sold by the fiber manufacturers, as final products, to commercial users or to other manufacturers where they are made into final products (Carey 2004).

Hesterberg and Hart (2001) reported that E glass was no longer produced as a microfiber in the United States and Europe but only as continuous filament (most of which are too thick to be respirable). JM753 also is a discontinued product (Angus Crane, personal communication to Sanford Garner, SRA, International, February 11, 2005).

2.2.3 Import and export of glass fibers

The United States International Trade Commission (USITC) reports information on imports and exports only by cost. The combined value of imports of insulation products consisting of the five product categories labeled (1) *mats, nonwoven, of glass fibers*; (2) *thin sheets (voiles), nonwoven, of glass fibers*; (3) *batts of nonwoven glass fibers*; (4) *pipe coverings of nonwoven glass fibers*; and (5) *other insulation products of nonwoven glass*

fibers varied considerably from 2000 to 2008 with a maximum value of $356 million in 2006 and a minimum value of $189 million in 2001; the value for 2008 was $196 million (USITC 2009a). The value of exports for the product category *insulation products of glass fibers* increased steadily from 2000 ($59 million) to 2008 ($121 million) [note that the product categories differ for imports and exports] (USITC 2009b). No category for special purpose fibers was identified for imports or exports.

2.3 Occupational exposures

Data from the latest U.S. Economic Census (USCB 2005) indicate that in 2002, there were 19,318 total workers (15,788 in manufacturing) employed within the North American Industrial Classification System (NAICS) code 327993, which "comprises establishments primarily engaged in manufacturing mineral wool and mineral wool (i.e., fiberglass) (*sic*) insulation products made of such siliceous materials as rock, slag, and glass or combinations thereof." [Based on the proportions of glass wool to other mineral wools used in the production of insulation products in North America (see Section 2.2.2), it is likely that the majority of the workers are involved in the manufacture of glass fibers.] The number listed for 2002 was slightly lower than in 1997 (21,610 total employees with 17,791 in manufacturing). OSHA estimated that there were more that 225,000 workers in the United States exposed to synthetic mineral fibers in manufacturing and end-use applications. Synthetic mineral fibers were defined as "fibrous inorganic substances made primarily from rock, clay, slag, or glass" (Maxim *et al.* 2003). No other national level data were found to estimate the total number of people exposed occupationally; [however, significant U.S. occupational exposure can be inferred through review of a combined cohort of production workers (Marsh *et al.* 2001a) (see Section 3.2.1.1)]. This cohort consisted of workers employed during the period from 1945 to 1978 in 8 plants that produced glass wool or glass wool and filament. In a 1992 follow-up evaluation, the cohort had a total of 26,679 workers.

The remainder of this section provides information on occupational exposure to glass fibers during their manufacture (Section 2.3.1), and from non-manufacturing activities (i.e., during installation or removal) (Section 2.3.2). The data on occupational exposures are reported for specific product types as presented in the source documents, and fiber

manufacturing methods and diameters are reported when available. Because of the importance of the non-U.S. occupational epidemiology studies that are presented in Section 3, non-U.S. exposure data are presented in this section following the U.S. data.

2.3.1 Exposure during manufacturing

Initial studies of airborne exposure to glass fibers were conducted in the late 1960s. These studies included gravimetric analysis and reported exposures in terms of mg/m^3. These early exposure studies (Corn *et al.* 1976, Corn and Sansone 1974, Esmen *et al.* 1978) demonstrated that similar mass-based exposures can result in highly variable fiber counts. This variability is determined by the fiber diameter distribution of the material. As a result, subsequent exposure assessments relied on fiber counts ($fibers/cm^3$) using optical (phase contrast) or electron microscopic methods of analysis. For the purposes of this report, only fiber count exposure estimates will be reported; however, fiber counts may vary between different studies depending on how a countable fiber was defined.

Production processes: glass fiber exposures and co-exposures

The air contaminants produced by the major production processes in glass fiber production facilities include the fibers themselves and other emissions associated with various processes (Smith *et al.* 2001). The exposure assessment by Smith *et al.* was conducted as part of the epidemiologic studies of Marsh *et al.* (2001c, 2001b, 2001a). Smith *et al.* also described the presence in the work areas of exposures other than the fibers themselves (Table 2-4) and identified co-exposures to substances that met the following criteria: (1) they are widely used, (2) there is a reasonable likelihood of exposure, (3) they have been used for more than 10 years, and (4) there must be a possible cancer risk, particularly lung cancer. Based on these criteria, the authors identified the following co-exposures in the synthetic vitreous fiber industry (listed in alphabetical order): aromatic hydrocarbons, arsenic, asbestos, asphalt, crystalline silica, epoxide compounds, formaldehyde, phenol (as a possible promoter), polycyclic aromatic hydrocarbons, radioactivity, styrene, and urea (as a possible promoter).

Table 2-4. Emissions from different production operations

Production operation[a]	Emissions[a]
Furnace: glass making	Furnace fume, trace metals, crystalline silica dust
Fiberizer: wool forming (nominal diameter)[b] staple forming (> 12 μm) steam blowing (5–12 μm) rotary blowing (< 2; 2–4; 4–8 μm) flame attenuation (< 2; 2-4 μm)	Airborne fibers[c] (concentration and size depend on nominal diameter), formaldehyde, aerosol of uncured phenol-formaldehyde binder
Curing oven/curing press	Formaldehyde, condensation oil aerosol, pyrolyis products, polycyclic aromatic hydrocarbons
Trimming and packaging	Fibers, resin particles, amorphous glass particles
Off-line fabrication	Fibers, resin particles, paint and amorphous glass particles
Material handling	Fibers, amorphous particles

Source: Smith *et al.* 2001.
[a]The authors noted that the list of operations and emissions was not exhaustive.
[b]The nominal diameter of the bulk fiber is determined by measuring the length-weighted size distribution. The common sizes produced by each type are also listed, but other sizes might be made.
[c]An airborne glass fiber was defined by the authors as < 5 μm in diameter with a length to width ratio > 3:1.

Glass fiber exposures in manufacturing facilities

One of the earliest studies of glass wool exposures was conducted in five manufacturing facilities (Johnson *et al.* 1969). Four of the five plants in this survey manufactured glass wool insulation. The fifth plant produced continuous glass filaments for textile fabrics. Results are presented as total fibers, fibers > 5 μm in length, fibers > 10 μm in length, and respirable fibers, which were collected using respirable-dust, size-selective inlets. Fiber concentrations (> 5 μm in length) within fiber operations collected in the glass wool plants without any size-selective inlet ranged from 0.0 to 1.01 fibers/cm^3. The range of concentrations for samples collected using respirable-dust inlets in the glass wool plants was 0.0 to 0.97 fibers/cm^3.

Dement (1975) surveyed fiber exposures in four glass wool production facilities manufacturing large-diameter (> 1 μm) insulation products and six plants manufacturing small-diameter (< 1.0 μm) glass fibers for use as filter paper and aircraft insulation. Analysis of the 167 samples collected from the four facilities manufacturing large-diameter insulation products showed mean fiber concentrations ranging from 0.04 to 0.2 fibers/cm^3. Based on 123 samples from the six plants manufacturing small-diameter glass

fibers, the mean airborne fiber concentrations ranged from 1.0 to 21.9 fibers/cm^3 across bulk fiber handling and fabrication/finishing operations.

Median airborne fiber diameters ranged from 1.1 to 4.3 μm and lengths ranged from 19 to 70 μm. Dement (1975) classified respirable fibers as being less than 3.5 μm in diameter and less than 50 μm in length. The percentage of fibers in the four glass wool manufacturing plants with diameter less than 3.5 μm ranged from 35% to 98% of the total fibers, while the percentage of fibers less than 50 μm in length ranged from approximately 40% to 91%. For the small-diameter fiber production facilities, the percentage of fibers less than 3.5 μm and the percentage of fibers less than 50 μm were not presented; however, across bulk-fiber–handling and fabrication/finishing operations for the 6 plants the percentage of fibers with diameters of less than or equal to 3.8 μm ranged from 89% to 100%, while the percentage of fibers less than or equal to 48 μm in length ranged from 70% to 97%. Dement concluded that based on the sampling data from this study, fiber concentrations in small-diameter fiber operations are many orders of magnitude higher than those levels seen in larger diameter fiber operations, and in addition, the smaller diameters and shorter lengths make the fibers more respirable.

The largest collection of U.S. glass wool manufacturing exposure data was gathered by Corn and Sansone (1974) and Esmen *et al.* (1979) in a series of studies in support of a large epidemiologic investigation (Enterline and Henderson 1975). Corn and Sansone reported the results of 115 air samples collected in three glass wool manufacturing facilities; however, one of the plants produced only fiberglass-reinforced plastics, and the data for this plant are not reported in Table 2-5. Phase contrast optical microscopy was used and fibers greater than 5 μm in length were reported (this is similar to NIOSH method 7400 A counting rules). The percentage of respirable fibers less than 3.5 μm in diameter and greater than 5 μm in length was also reported. Overall mean fiber concentrations (greater than 5 μm in length) ranged from 0.02 to 1.41 fibers/cm^3. The highest fiber concentration was 3.16 fibers/cm^3 measured in a filter tube finishing operation. The percentage of fibers in the respirable range was highly variable but generally ranged from 20% to 60%.

Esmen *et al.* (1979) reported on the exposures of U.S. production workers in 16 facilities that produced glass wool, glass filament, rock wool, and slag wool products. Seven of the plants studied produced glass wool (two of the seven facilities also produced continuous glass filament); for the plants that produced only loose glass fibers, the nominal diameters ranged from 3 to 10 μm. One facility produced glass fibers with nominal diameters ranging from 0.05 to 1.6 μm [fiber diameters that are generally associated with special-purpose glass fibers], and one facility received fibers with nominal diameters ranging from 7 to 10 μm from another facility and prepared the fibers for manufacturing [fabrication]. Across several plant operations, the overall mean concentrations across the eight facilities manufacturing or fabricating the larger diameter fibers ranged from 0.0094 to 0.042 fibers/cm^3 for fibers greater than 5 μm in length. Mean exposure levels in the plant producing small-diameter fibers ranged from 0.0097 to 1.56 fibers/cm^3 with an overall mean of 0.78 fibers/cm^3.

In another study, Esmen *et al.* (1982) evaluated airborne exposure levels of fine-diameter fibers in a facility that manufactured aircraft insulation products. Mean airborne respirable-fiber concentrations ranged from 0.05 to 1.7 fibers/cm^3. The highest single concentration observed was 3.8 fibers/cm^3.

A follow-up study of five of the nine glass fiber plants surveyed by Esmen *et al.* (1979) was reported in 1984 (Hammad and Esmen 1984). Four of the facilities produced large-diameter fibers (nominal diameters ranging from 1 to 15 μm) and one facility produced small-diameter glass fibers (nominal diameters ranging from 0.05 to 1.6 μm). For the large-diameter production facilities, across various areas of the production facilities, mean fiber concentrations ranged from 0.0047 to 2.22 fibers/cm^3. (The value of 2.22 fibers/cm^3 was from the quality control area of one of the facilities; the next highest mean value at this facility was 0.46 fibers/cm^3.) For the facility producing small-diameter fibers, mean fiber concentrations ranged from 0.048 to 6.77 fibers/cm^3 across production areas.

Smith *et al.* (2001) summarized estimated airborne glass fiber exposure levels from the production of insulation glass wool mats and small-diameter fibers for two time periods:

before 1980 and after 1980. Plant-level mean concentrations for insulation glass wool production ranged from 0.045 to 0.262 fibers/cm^3 and the simple mean of the plants combined was 0.15 fibers/cm^3 for the period before 1980. For the period after 1980, plant means ranged from 0.026 to 0.278 fibers/cm^3 with a simple mean for the plants combined of 0.091 fibers/cm^3. For small-diameter fibers, plant-level mean concentrations for the period before 1980 ranged from 0.027 to 1.94 fibers/cm^3 with a simple mean for the plants combined of 0.662 fibers/cm^3. Exposure levels measured after 1980 ranged from 0.025 to 1.86 fibers/cm^3 with a simple mean of 0.745 fibers/cm^3 for the plants combined.

In collaboration with the North American Insulation Manufacturers Association (NAIMA), Marchant *et al.* (2002) summarized exposure data collected or commissioned by NAIMA. As part of the Health and Safety Partnership Program (HSPP) (see Section 2.6.2), NAIMA developed an occupational exposure database for SVF. Existing exposure data were collected from various sources and NAIMA or its member companies commissioned new exposure monitoring studies. Various sampling and analytical methods were used for the data that were collected; however, only fibers meeting the NIOSH 7400B rule were included in the results presented by Marchant *et al*. In addition, only personal sampling results for periods of at least 240 minutes were included in the results. Means of samples collected in glass wool manufacturing and fabrication environments (N = 2,304), ranged from 0.03 to 0.16 fibers/cm^3. Data were also provided for several product categories generally associated with special purpose fiber applications. For example, for aircraft insulation manufacturing, the mean respirable fiber concentration was 0.06 fibers/cm^3 for primary manufacturing, 0.03 fibers/cm^3 for secondary manufacturing, and 0.13 fibers/cm^3 for fabrication. Filtration products had a mean concentration of 0.22 fibers/cm^3 for primary manufacturing, 0.02 fibers/cm^3 for secondary manufacturing, and 1.15 fibers/cm^3 for fabrication.

Exposure levels similar to those reported in the U.S. studies have been reported in non-U.S. studies. In a large survey of occupational exposures to MMVF, Head and Wagg (1980) assessed respirable fiber levels in 25 plants and construction sites in the United Kingdom, including 3 insulation glass wool manufacturing facilities and 4 facilities that manufactured glass fiber paper and filtration products using special-purpose fibers.

Respirable fibers were defined as those with a diameter of less than 3 μm and length greater than 5 μm. Overall mean respirable fiber concentrations across the 3 insulation glass wool plants ranged from 0.12 to 0.31 fibers/cm^3, while individual samples ranged from 0.003 to 1.1 fibers/cm^3. For special-purpose fibers, overall mean concentrations ranged from 0.08 to 3.70 fibers/cm^3, while individual samples ranged from 0.02 to 18.83 fibers/cm^3. The maximum fiber count was found at a paper-slitting machine. The authors noted that higher dust levels were found at conversion processes (where fibers are converted to finished products) due to the greater degree of manipulation of the materials.

In support of a large European occupational epidemiologic study of MMVF, the Institute of Occupational Medicine, in Edinburgh, U.K., measured the concentrations of airborne MMVF fibers in 13 European production plants, including 4 glass wool plants. The results of this analysis were initially reported by Ottery *et al*. (1984); however, the sampling results were reanalyzed using a different counting method and determined to be too low by about a factor of 2.2. The results of the reanalysis were reported in Cherrie *et al.* (1986) and these results are presented in Table 2-5. The authors noted that the maximum mean concentration was associated with the manufacture of special fine fiber earplugs. [It is likely that these levels were associated with special-purpose fibers; however, Cherrie *et al.* did not specify categories for glass wool fibers, and the facility for which these levels were associated produced both insulation wools and "special fine fiber earplugs."]

Krantz (1988) *et al*. reported the results of an analysis of occupational exposure to SVF in 9 Swedish factories that produced insulation wools (rock or glass wools) or special-purpose fiber products. Personal sampling was performed usually over two full shifts with sampling time varying between 2 and 8 hours depending on operation and fiber level. Fiber counting was performed using phase-contrast optical microscopy; respirable fibers were defined as having an aspect ratio of 3, a diameter equal to or less than 3 μm, and a length of 5 μm or greater. The results for the two categories of fiber are presented in Table 2-5. The authors noted that for both insulation wools and special-purpose fibers the maximum median diameter for airborne glass fibers was below 1 μm, and that when this value was compared with the nominal fiber diameter of the product, it was obvious

that it was the fine (thin) fibers in the product that became airborne. It was also noted that, for the whole study, between 73% and 94% of the airborne fibrous dust was respirable.

Yeung and Rogers (1996) reported the results of a large study reviewing the national profile of occupational exposure to SVF, including glass wool, in Australia. SVF data consisting of 1,572 samples from 252 sampling activities was collected by standardized questionnaire from a number of different sources throughout Australia, including government agencies, occupational health and safety consultants, SVF manufacturers and end-users, and academia. All data were validated for technical integrity and it was also noted that 87% of the sampling results were analyzed in accredited laboratories. The authors reported that the nominal diameter of glass wool typically ranged between 5 and 8 μm and that between 10% and 20% of fibers in the product were less than 3 μm in diameter. Based on 94 samples, the geometric mean fiber concentration was 0.03 fibers/cm^3, and the range across all samples was from less than 0.01 fibers/cm^3 to 0.2 fibers/cm^3.

In 1990, an Australian standard was established of 0.5 fibers/cm^3 for all forms of MMVF. Yeung and Rogers compared sampling data from before the establishment of the regulatory limit with data collected after its establishment and noted that no quantitative trend or difference in airborne exposure levels between the two time periods was apparent.

Table 2-5. Occupational exposure to glass fibers in production facilities using phase contrast microscopy

Reference	Sample Description	Fiber Definition	Exposure Levels (fibers/cm^3)
U.S. data			
Johnson *et al.* 1969	Personal samples from workers in four plants manufacturing glass wool insulation products.	Aspect ratio not specified[a] Total fibers > 5 μm in length	0.0–1.01 (range of individual samples)
Dement 1975	Glass fiber exposures of workers in four glass wool production facilities manufacturing large-diameter (> 1 μm) insulation products (A, B, C, D) and six facilities manufacturing small-diameter (< 1 μm) glass fiber products (C, E, F, G, H, I) [Plant C produced both large and small diameter fibers]	Aspect ratio not specified[a] Total fibers > 5 μm in length	*Large-diameter (> 1 μm) fiber plants* 0.04–0.2 (range of means) *Small-diameter (< 1 μm) fiber plants* 1.0–21.9 (range of means)
Corn and Sansone 1974	Personal samples from workers in three glass wool manufacturing facilites, conducted in support of large epidemiologic study of SVF Plants A and B manufactured various products, including insulation; however, Plant C produced only fiberglass-reinforced plastics. Results presented for A and B only.	Aspect ratio not specified[a] Total fibers > 5 μm in length	Plant A 0.03–0.08 Plant B 0.02–1.41 (range of means)
Esmen *et al.* 1979	Personal sampling of airborne exposure levels in 5 large-diameter (1–12 μm) glass fiber production facilities, 2 large-diameter glass fiber and continuous filament production facilities, 1 large-diameter glass fiber fabrication facility, and 1 small-diameter glass fiber production facility from 1975–1978	Aspect ratio not specified[a] Total fibers > 5 μm in length	0.0094–0.042 (range of overall means of 8 large diameter manufacturing/fabricating facilities)

Reference	Sample Description	Fiber Definition	Exposure Levels (fibers/cm^3)
Esmen *et al.* 1982	Airborne glass fiber exposure to fine-diameter fibers during manufacture and fabrication of aircraft insulation products in 2 facilities (A & B) Average nominal fiber diameter in plant A = 1 μm; not reported for plant B	Aspect ratio not specified[a] Length > 5 μm Diameter < 3 μm	0.05–1.7 (range of means)
Hammad and Esmen 1984	Follow-up study of 5 of the 9 glass wool production facilities sampled in Esmen *et al.* (1979) Plant 1: wool insulation and continuous filament (nominal diameters 5–15 μm) Plant 2: insulation products (nominal diameters 6–10 μm) Plant 3: insulation and flotation wool, filtration media (nominal diameters 1–6 μm) Plant 4: wool insulation and continuous filament (nominal diameters 1–12 μm) Plant 5: very fine fibrous glass for filtration media, thermal insulation, and aerospace applications (nominal diameters 0.05–1.6 μm)	Aspect ratio not specified[b]	Plant 1 0.0047–0.028 Plant 2 0.015–0.062 Plant 3 0.012–2.22 (next highest 0.46) Plant 4 0.010–0.28 Plant 5 0.048–6.77 (range of means)
Marsh *et al.* 2001a	Estimated exposures of U.S. man-made vitreous fiber cohort of fiberglass mat and board insulation operations workers from 1970 to 1987 in 5 plants producing mostly glass wool	Aspect ratio > 3:1 Length > 5 μm Diameter < 3 μm	0.049–0.211 (range of means)
Smith *et al.* 2001	Airborne glass fiber exposures in 4 plants manufacturing insulation wool and small-diameter fibers	Aspect ratio > 3:1 Length > 5 μm Diameter < 3 μm	*Insulation glass wool* 0.045–0.262 (range of means before 1980) 0.026–0.278 (range of means after 1980) *Small diameter fibers* 0.027–1.94 (range of means before 1980) 0.025–1.86 (range of means after 1980)

Reference	Sample Description	Fiber Definition	Exposure Levels (fibers/cm^3)
Marchant *et al.* 2009 [data collected or commisioned by NAIMA]	Exposure levels for primary and secondary manufacturing and fabrication in the glass wool industry sector as a whole and for product categories: aircraft insulation, appliance insulation, duct insulation, filtration products, and pipe insulation [product categories not separated by glass wool and rock/slag wool]	Aspect ratio ≥ 5:1 Length > 5 μm Diameter < 3 μm	*Overall glass wool production* 0.03–0.16 (range of means) *Filtration products manufacturing* 0.02–1.15 (range of means) *All other product manufacturing types* 0.03–0.13 (range of means)
Non-U.S. data			
Head and Wagg 1980 U.K.	Occupational exposures across 3 insulation glass wool manufacturing plants Exposure levels across 4 production facilities using glass micro-fibers in the manufacture of high-efficiency filters	Respirable fibers: Aspect ratio ≥ 3 Length > 5 μm Diameter < 3 μm	*Insulation glass wool manufacturing* 0.12–0.31 (range of means across plants) 0.003–1.10 (range of ind. samples) *Glass microfiber manufacturing* 0.08–3.70 (range of means across plant/product combinations) 0.02–18.83 (range of individual samples)
Cherrie *et al.* 1986 (update of Ottery *et al.* 1984) Europe	Surveys of 4 glass wool plants. Mean values range across 7 job categories	Respirable fibers:[c] Aspect ratio ≥ 3 Diameter < 3 μm Length ≥ 5 μm	0.01–1.0 (range of means) 0.01–4.02 (range of ind. samples)
Krantz 1988 Sweden	Personal sampling in nine factories that produced insulation wools (rock and glass) and/or special-purpose glass fiber products (earplugs): number of facilities not specified by type of product	Respirable fibers: Aspect ratio ≥ 3 Diameter ≤ 3 μm Length ≥ 5 μm	*Insulation wools* 0.18 (mean across all jobs/facilities) 0.01–1.8 (range of individual samples across all jobs/facilities) *Special-purpose glass fibers products* 0.47 (mean across all jobs/facilities) 0.08–2.4 (range of individual samples across all jobs/facilities)

Reference	Sample Description	Fiber Definition	Exposure Levels (fibers/cm^3)
Yeung and Rogers 1996 Australia[d]	Levels for fiberglass manufacturing across all jobs/processes. Data collected by standardized questionnaire and includes both personal and stationary sampling	Respirable fiber Aspect ratio: 3 Length > 5 μm Diameter < 3 μm	0.03 (geometric mean) < 0.01–0.2 (range of individual samples)

ind. = individual; NR = not reported.
[a]Assumed to be 3:1.
[b]Assumed to be the same as Esmen *et al.* 1979.
[c]Study is an update of Ottery *et al.*, and the fiber definiton came from that paper.
[d] Phase contrast microscopy not specified for these data.

2.3.2 Non-manufacturing occupational exposures

Exposures can occur while installing, removing, fabricating, or otherwise working with glass wool outside the manufacturing environment. These applications are sometimes referred to as end-use, and workers engaged in these applications, therefore, can be referred to as end-users. Since glass wool is primarily used for insulation purposes, most of the end-use exposure data focuses on insulation activities. Exposures in these end-user applications are typically higher than in the fiber manufacturing environments.

As cited by Maxim *et al.* (2003), the United States Department of Labor (USDOL), Bureau of Labor Statistics (BLS) (2009), reported that approximately 53,000 workers were employed by insulation contractors in the year 2000. This number was projected to grow to 60,000 by 2010. In May, 2007 the U.S. Bureau of Labor Statistics reported that nearly 31,000 workers were employed as "insulation workers" within the NAICS Code 238310 (Drywall and Insulation Contractors). Additionally, workers involved in other construction trades such as drywall installers, carpenters, and heating and cooling specialists also install insulation. Approximately 150,000 of these workers have periodic exposure to glass wool insulation materials (Maxim *et al.* 2003). Lees *et al*. (1993) cited OSHA estimates that in 1992, there were 185,000 full-time–equivalent construction workers employed in the U.S. residential insulation trades.

Residential homeowners engaged in home remodeling projects are potentially exposed to insulation materials through the removal and replacement of existing products. No data were identified regarding the number of individuals involved in these activities, although the majority of these projects involve the installation of batt and/or blanket insulation, rather than loose fill insulation (Maxim *et al.* 2002).

Fowler *et al.* (1971) sampled a variety of fiberglass insulating operations, including duct wrapping, wall and plenum insulation, pipe insulation and fan housing insulation. Task-length average (20 to 60 minutes) total fiber concentrations ranged from 0.48 to 8.08 fibers/cm^3 with a median of 1.26 fibers/cm^{3}and a mean of 1.8 fibers/cm^3. Fowler *et al.* estimated that about half of the airborne fibers generated during installation were less than 3.5 μm in diameter. Mean exposure levels to workers of other trades working close to the insulation operations were 0.1 fibers/cm^3.

Worker exposure to glass wool during the installation of commercial and residential insulation in buildings and at two aircraft insulation facilities was evaluated by Esmen *et al.* (1982). The average respirable fiber exposure of workers for all applications, except the blowing of thermal insulation into attics, ranged from 0.003 to 0.13 fibers/cm^3. Average respirable glass wool exposures during blowing attic insulation ranged from 0.31 to 1.8 fibers/cm^3. The range of individual exposure levels for the blower was 0.67 to 4.8 fibers/cm^3.

Jacob *et al.* (1992) characterized the task-length (typically 1 to 2 hours) fiber concentrations during the installation of residential glass wool insulation in 13 cities throughout the United States. Jacob *et al.* reported results as a combination of counting fibers deposited on the filter and rinsed from the cowl. A cowl-rinsing procedure reported by Breysse *et al.* (1990) was used to evaluate the deposition of fibers on the inside of the collection cowl. The average fraction of fibers on the cowl was reported to be 25% of the total fiber counts. Based on differential counting, Jacob *et al.* reported total respirable fibers as well as respirable glass wool fibers (fiber identity based on morphology and polarized light). Glass fibers were found to account for between 40% and 70% of the respirable fibers. Mean respirable-fiber exposure during the installation of batt insulation was 0.059 fibers/cm^3 with a 95% confidence interval of 0.049 to 0.073 fibers/cm^3. Mean respirable-fiber exposures during blowing wool insulation ranged from 0.12 to 0.91 fibers/cm^3 with the installers having the highest mean exposures.

Lees *et al.* (1993) conducted a comprehensive residential insulation installation exposure survey in the early 1990s. Workers were monitored during insulation operations in 107 houses in 11 different states, and results were presented as task-length averages. Similar to Jacob *et al.* (1992), fiber counts included fibers deposited on the inside of the conducting cowl. Lees *et al.* (1993) reported respirable fiber (NIOSH 7400B rules) concentrations during installation of glass wool batt insulation in homes ranging from 0.02 to 0.42 fibers/cm^3, with a mean of 0.14 fibers/cm^3. The installation of loose fiberglass insulation resulted in mean exposures of 0.55 fibers/cm^3 for the installer and 0.18 fibers/cm^3 for the feeder. The highest exposures were noted for installation of loose insulation without binder. For installers, exposure levels ranged from 1.32 to 18.4

fibers/cm^3, with a mean of 7.67 fibers/cm^3, while for feeders, levels ranged from 0.06 to 9.36 fibers/cm^3, with a mean of 1.74 fibers/cm^3.

More recently, Marchant *et al*. (2009) reported an overall mean SVF exposure level during glass wool installation operations of 0.39 fibers/cm^3 and a mean level of 0.26 for retrofit/removal operations. In a task-exposure analysis, the mean batt insulation installation exposure level was 0.11 fibers/cm^3, while the mean loose-fill insulation installation exposure level was 0.51 fibers/cm^3. Fiber counting was conducted using NIOSH B rules.

In addition to residential and building insulation, glass wool is fabricated for and used in a variety of other commercial products. Jacob *et al.* (1993) evaluated glass wool exposures in eleven different end-user manufacturing environments, including the fabrication and assembly of metal building and manufactured housing insulation, pipe insulation, small appliance manufacturing, air handling ducts, and water heaters. The mean concentration of respirable fibers ranged from 0.006 to 0.087 fibers/cm^3. These counts included fibers rinsed from the cowl.

There are limited data on exposures during glass wool removal. Jacob *et al.* (1993) assessed exposures during pipe and ceiling board removal. The arithmetic mean total fiber exposure was 0.29 fibers/cm^3 with a 95% confidence interval of 0.2 to 0.41 fibers/cm^3.

Breysse *et al.* (2001) reported end-user glass wool exposures in a variety of commercial applications. Applications sampled included duct board, duct liner, duct wrap fabrication and installation, and pipe insulation installation. Fiber concentrations were reported according to NIOSH 7400B counting rules and included cowl fibers. The addition of cowl fibers increased concentrations by 35% to 47%. Mean end-user fiber concentrations ranged from 0.05 to 0.68 fibers/cm^3. The highest fiber concentrations, from 0.17 to 2.13 fibers/cm^3, were found during duct wrap insulation installation.

Exposure levels similar to those reported in the U.S. studies have been reported in non-U.S. studies (Head and Wagg 1980, Perrault *et al.* 1992, Yeung and Rogers 1996).

Head and Wagg (1980) studied airborne concentrations of respirable insulation glass wool fibers in 3 manufacturing plants and 2 construction sites in the United Kingdom, and reported slightly higher levels among non-production workers than for production workers. The maximum mean level for installation of fiberglass insulation blankets in a domestic loft was 1.02 fibers/cm^3 with a maximum individual level of 1.76 fiber/cm^3.

In the early 1990s an occupational exposure survey of MMVF insulation products was conducted at several industrial construction sites in Montreal, Canada where workers were installing or removing insulation (Perrault *et al.* 1992). For glass wool, two sites were investigated: one site where refractory fibers and glass wool products were being installed and another site where only glass wool insulation was being installed. Results for the glass-wool only facility are presented in Table 2-6.

As discussed earlier, Yeung and Rogers (1996) reported the results of a large study to review the national profile of occupational exposure to MMVF in Australia. MMVF exposure data, including data from installation and removal activities, were collected by standardized questionnaire from a number of different sources throughout Australia. For non-manufacturing exposures, slightly higher levels were reported for glass wool installation compared with removal (maximum geometric mean of 0.12 fibers/cm^3 versus 0.04 fibers/cm^3 and maximum individual sample of 0.8 fibers/cm^3 versus 0.2 fibers/cm^3). Levels associated with glass wool removal were similar to levels associated with production, which had a geometric mean concentration of 0.03 fibers/cm^3 and a range of less than 0.01 to 0.2 fibers/cm^3.

Table 2-6. Non-manufacturing occupational exposure to glass wool using phase contrast optical microscopy

Reference	Sample Description	Fiber Definition	Exposure Levels (fibers/cm^3)
U.S data			
Fowler *et al.* 1971	Fiberglass insulating operations including duct wrapping, wall and plenum insulation, pipe insulation, and fan housing insulation	total fibers	0.48–8.08 (range of individual samples)
Esmen *et al.* 1982	Worker exposure to glass wool during the installation of commercial and residential insulation in buildings	aspect ratio not specified length > 5 μm diameter < 3 μm	0.003–1.8 (range of means)
Jacob *et al.* 1992	Fiber concentrations during the installation of residential glass wool insulation in 13 cities throughout the U.S. (includes fibers rinsed from cowl)	aspect ratio ≥ 5:1 length > 5 μm diameter < 3 μm	0.059–0.91 (range of means)
Lees *et al.* 1993	Worker exposure during residential insulation operations (includes fibers rinsed from cowl)	aspect ratio ≥ 5:1 length > 5 μm diameter < 3 μm	0.14–7.67 (range of means)
Jacob *et al.* 1993	Glass wool exposures in eleven different end-user manufacturing environments (includes fibers rinsed from cowl)	aspect ratio ≥ 5:1 length > 5 μm diameter < 3 μm	0.006–0.087 (range of means)
Breysse *et al.* 2001	End-user glass wool exposures in a variety of commercial applications (includes fibers rinsed from cowl)	aspect ratio ≥ 5:1 length > 5 μm diameter < 3 μm	0.05–0.68 (range of means)
Marchant *et al.* 2009	Exposure levels from glass wool insulation installation operations collected or commisioned by NAIMA	aspect ratio ≥ 5:1 length > 5 μm diameter < 3 μm	0.39 (mean, installation) 0.26 (mean, retrofit/removal)

Reference	Sample Description	Fiber Definition	Exposure Levels (fibers/cm^3)
Non-U.S data			
Head and Wagg 1980 U.K.	Occupational exposure sampling during installation of fiberglass blanket insulation at two sites	respirable fibers: length > 5 µm diameter < 3 µm	0.38 & 1.02 (mean levels for two sites) 0.24–1.76 (range of individual samples across sites)
Perrault *et al.* 1992 Canada	Sampling performed at a construction site during installation of fiberglass insulation.	respirable fiber length > 5 µm diameter < 3 µm aspect ratio: 3	0.01 (geometric mean)
Yeung and Rogers 1996)[a] Australia	Levels for installation and removal of fiberglass insulation products: data collected by standardized questionnaire and includes both personal and stationary sampling	respirable fiber length > 5 µm diameter < 3 µm aspect ratio: 3	*Installation* 0.06 (<0.01–0.8) (geometric mean and range) *Removal* 0.03 (<0.01–0.2) (geometric mean and range)

[a] Phase contrast microscopy not specified for these data.

2.4 Environmental occurrence and general population exposure in the United States

No information was identified on environmental occurrence and exposure to specific glass fiber products; therefore, most of the data presented in this section are from occurrence and exposure to SVFs as a group.

SVFs do not occur naturally in the environment, but they may be released into the environment during production, installation, use, removal, and disposal. Additionally, SVFs and glass fibers were found in air and dust samples following the terrorist attacks on the World Trade Center in September, 2001. [It also is likely that elevated levels could be seen due to building implosions or structure fires.] Like other inorganic substances, SVFs do not undergo typical transformations in the environment, such as photolysis and biodegradation. As described in Section 1, SVFs are reasonably soluble under acidic or alkaline conditions, dissolving about 2 to 4 times quicker than crystalline fibers such as asbestos. The transport and partitioning of SVFs are largely governed by fiber size, with large fibers removed from air and water by gravitational settling at a rate dependent upon their size. Small fibers may remain suspended for long periods of time.

The primary route of SVF release into the environment is through the air. There are no published data on quantities of SVFs released into the environment in the United States, and there are no published data on contamination of soil, water, or food by SVFs. There are limited data on general population non-occupational exposures to SVFs. [Non-occupational exposures might occur during do-it-yourself home remodeling activities due to release of glass wool fibers from insulation and building materials.]

Jacob *et al.* (1992) measured airborne glass wool concentrations before and after insulation installation. Post-installation mean respirable fiber concentrations were low, ranging from 0.002 fibers/cm^3 for batt installation to 0.001 fibers/cm^3 for blowing wool operations. Post-installation concentrations were not significantly different from pre-installation concentrations.

2.4.1 Indoor and ambient levels

In order to assess the fiber release from air ducts lined with fiberglass, Balzer *et al.* (1971) measured fiber levels in 13 buildings. Results suggest that there was no increase

in fiber concentration due to air passing through ducts lined with fiberglass. Additionally, Balzer *et al.* found that the glass fiber concentration outside of the buildings averaged 0.0002 fibers/cm^3.

Miller *et al.* (1995) analyzed the fiber concentrations in living spaces of 14 homes both prior to installation of insulation and again the evening following installation. Total fibers were measured at levels ranging from < 0.001 to 0.009 fibers/cm^3 before installation, and from 0.03 to 0.012 fibers/cm^3 1 day post-installation using phase-contrast microscopy and NIOSH 7400B counting rules. The mean living-space fiber concentrations were not significantly elevated after installation. Similar results were obtained when using scanning electron microscopy to count only SVFs. These results suggest airborne fiber concentrations diminish rapidly following installation.

In order to evaluate concern that the erosion of SVFs from insulation materials may contribute to fiber levels in the indoor environment, Carter *et al.* (1999) collected 205 area samples in 51 residential and commercial buildings. Twenty-one air samples were collected simultaneously outdoors at 19 buildings. All samples were analyzed by phase-contrast microscopy following the NIOSH 7400 B counting rules. The mean value for all respirable indoor fibers was 0.008 fibers/cm^3 with a median value of 0.007 fibers/cm^3 and a maximum value of 0.029 fibers/cm^3. Ninety-seven percent of the respirable fibers identified by scanning electron microscopy with energy-dispersive X-ray microanalysis (SEM-EDX) were determined to be organic. MMVF were detected in only two samples. The median of the outdoor samples collected at nineteen different locations was < 0.001 fibers/cm^3 and individual samples ranged from < 0.001 to 0.009 fibers/cm^3.

Switala *et al.* (1994) assessed the concentration of respirable glass fibers near a large fiberglass wool manufacturing facility in an urban area, and also in a rural area, both in Ohio. Airborne glass fiber concentrations based on phase-contrast microscopy and NIOSH 7400B rules ranged from < 1.0×10^{-5} to 1.4×10^{-4} fibers/cm^3. These levels were similar to the measured levels in ambient air from a rural site located 10 miles away from the plant. The concentration of glass fiber concentrations at the rural location ranged from

$< 1.0 \times 10^{-5}$ to 1.5×10^{-4} fibers/cm^3, during the same sampling period. Glass fibers accounted for < 1% of the total respirable fibers measured at these sites.

2.4.2 World Trade Center levels

Following the terrorist attacks on the World Trade Center (WTC) in New York City on September 11, 2001, numerous local and Federal agencies undertook environmental sampling initiatives to characterize the environmental exposures resulting from destruction of the WTC and to assess related health effects (Landrigan *et al.* 2004, Lioy *et al.* 2002, Lowers *et al.* 2009, MMWR 2003, Tang *et al.* 2004). Shortly after the attacks, simultaneous sampling efforts were undertaken to assess the level of various contaminants, including SVF and glass fibers, in air and dust of impacted areas and in minimally impacted areas north of the WTC to establish baseline levels.

Lioy *et al.* (2002), reported the results of samples that were taken on September 16 and 17 from three undisturbed locations within a mile of the WTC site: the samples were taken from locations that were protected from the rain that occurred on September 14. All three samples consisted of 40% glass fibers (mass percentage) with the remaining mass for the three samples consisting of varying amounts of nonfiber material (cement/carbon), cellulose, and chrysotile asbestos. Landrigan *et al.* (2004) also noted that morphologically, most of the dust samples resulting from the WTC event were fibrous and contained mineral wool, glass fibers, asbestos, wood, paper, and cotton fibers. The authors suggested that compounds and materials present in the plume would be similar to those found in plumes from building fires or building implosions.

Exposure from the WTC event was primarily from inhalation or ingestion of dust directly after the event or due to resuspension of dust during clean-up activities following the event (Landrigan *et al.* 2004, Lioy *et al.* 2002). Firefighters, police, and other first responders sustained the heaviest initial exposures. Airborne exposures in the residential and business communities of lower Manhattan, beyond Ground Zero, were much lower than those sustained by workers. Additional indoor exposure to residents may have also occurred from resuspended residual dust remaining in the residence or from ventilation systems not properly cleaned.

In a study to characterize the background levels of contaminants identified in dust related to the collapse of the WTC towers, sampling was performed at locations that were minimally impacted by the dust fallout (Tang *et al.* 2004). Indoor dust and air samples were collected in 25 residential units and 9 building interior common areas within 14 buildings. The authors noted that SVF was detected at very low levels and that many samples tested below the limit of detection. The authors noted that these values were in agreement with levels found in the literature. No data specific for glass fibers were presented.

Studies reporting general population exposures to airborne glass fibers in ambient air are summarized in Table 2-7.

Table 2-7. General U.S. population exposure to glass wool in ambient air using phase contrast optical microscopy

Reference	Sample Description	Fiber description	Exposure Levels (fibers/cm^3)
Balzer *et al.* 1971	Airborne fiber concentrations both inside and outside 13 buildings with fiberglass-lined duct work	Fiber counting technique pre-dates any of the current specifications	No increase in glass fiber concentration due to air passing through ducts lined with fiberglass. The average glass fiber concentration outside the buildings was 0.0002
Jacob *et al.* 1992	Airborne glass wool concentrations before and several hours after insulation installation	Aspect ratio ≥ 5:1 Length > 5 μm Diameter < 3 μm	Batt insulation: Mean fiber conc. before installation: 0.002; mean fiber conc. after installation: 0.001 Blowing wool operations: Mean fiber conc. before installation: 0.001; mean fiber conc. after installation: 0.001
Switala *et al.* 1994	Airborne respirable glass fiber concentrations near a large glass wool production facility, and in a rural location	Aspect ratio ≥5:1 Length > 5 μm Diameter < 3 μm	Outside plant: < 1.0×10^{-5}–1.4×10^{-4}
			Rural: < 1.0×10^{-5}–1.5×10^{-4}
Miller *et al.* 1995	Airborne fiber concentrations in the living areas of 14 homes both before and approximately 24 hours after glass wool insulation installation	Aspect ratio ≥ 5:1 Length > 5 μm Diameter < 3 μm	Before installation: < 0.001–0.009
			24 hours after installation: 0.03–0.012
Carter *et al.* 1999	Airborne fiber concentrations in 51 residential and commercial buildings with fiberglass insulation materials and simultaneous outdoor sampling at 19 sites	Aspect ratio ≥5:1 Length > 5 μm Diameter < 3 μm	Inside buildings: Mean: 0.008 Median: 0.007 Maximum: 0.029
			Outside buildings: < 0.001–0.009

conc. = concentration.

2.5 Biological indices of exposure

There are no traditional biological indices of exposure for SVFs, as these are not compounds that metabolize or break down in the body in the usual sense. Assessment of biological exposure to SVFs has been attempted through the measurement of fiber retention in human lung tissue (IARC 2002). In a study of autopsies of glass, rock, and slag wool workers in the United States, analytical transmission electron microscopy was used to determine retention of fibers in the lung 12 years since the end of exposure. No significant difference was observed between SVFs in the lungs of 112 production workers (101 glass wool and 11 rock or slag wool workers) or controls (112 consecutive autopsies from the same hospital) in the study. The authors concluded that either the SVFs disappeared from the lungs in less than 12 years, the workers did not inhale enough SVFs to result in a difference when compared with the controls 12 years after the end of the exposure, or the fixative fluids used for the lungs could have altered some retained fibers (IARC 2002).

In a study investigating a possible biomonitoring method for SVF exposure, Paananen *et al*. (2004) performed nasal lavage on workers from 2 factories and measured concentrations of MMVF by electron microscopy. Cytokines (IL-6, IL-8, TNF-alpha, and IFN-gamma) were also assayed, and inflammatory cells (lymphocytes, eosinophils, neutrophils, and macrophages) were counted microscopically. In nasal lavage samples, the mean concentration of MMVF (length > 1.5 μm) was 3,260 fibers/cm^3 in factory 1, 11,680 fibers/ cm^3 in factory 2, and below 55 fibers/ cm^3 in the control group. The group-specific mean concentration of MMVF in nasal lavage samples correlated with production rates and airborne fiber levels in both plants. No significant differences in the biological response (inflammatory cells, cytokines) were found between the groups exposed and the control group. The authors concluded that nasal lavage could be used as a biomonitoring method in the assessment of MMVF exposure.

2.6 Regulations and guidelines

2.6.1 Regulations

U.S. Environmental Protection Agency (EPA)

Clean Air Act

NESHAP: Fine mineral fiber emissions from facilities manufacturing or processing glass (of average diameter 1 micrometer (μm) or less) is listed as a Hazardous Air Pollutant (HAP)

NSPA: Manufacturers of wool fiberglass are subject to provisions of NSPS for the control of particulates as prescribed in 40 CFR 60.292 and 293.

Occupational Safety and Health Administration (OSHA)

Permissible Exposure Limit (PEL) = 15 mg/m^3 (total); 5 mg/m^3 (respirable) (based on regulation for "particulates not otherwise regulated")

2.6.2 Guidelines

American Conference of Governmental Industrial Hygienists (ACGIH)

Threshold Limit Value - Time-Weighted Average Limit (TLV-TWA) =1 fiber/cm^3 (respirable fibers)

National Institute for Occupational Safety and Health (NIOSH)

Recommended Exposure Limit (REL) = 3 fibers/cm^3 (fibers with diameter ≤ 3.5 μm & length ≥ 10 μm); 5 mg/m^3 (total) (listing is for "fibrous glass dust")

Occupational Safety and Health Administration (OSHA)

Health and Safety Partnership Program (HSPP) for manufacturers:

Maximum concentration of 1 WHO fiber/cc (cm^3), 8 hour TWA for respirable SVF (WHO fiber is a fiber with diameter < 3 μm, length ≥ 5 μm and length to diameter ratio ≥ 3:1)

2.7 Summary

The vast majority of SVF produced and used in the United States consists of glass wool used for home and building insulation. Small amounts of glass fibers are produced for special applications such as use in battery separator media, high-efficiency filters, and aircraft insulation. Glass wool is produced by heating the glass to high temperatures, extruding the molten glass to form small streams of glass fibers, and using centrifugal force to attenuate the streams of glass into glass fibers. Finer fibers are formed by flame attenuation. Most general purpose insulation glass wools have nominal diameters ranging from 1 to 10 μm, while special-purpose fibers generally range from 0.1 to 3 μm;

however, product bulk samples may have fibers with diameters that are several times greater or smaller than the nominal diameters. ACGIH noted that because of this variation, all wool fiber products contain respirable fibers. The physical properties of fibers affect their likelihood of becoming airborne, with smaller fibers more likely to become airborne. Because of this, the average diameter and length may be smaller and the percentage of respirable fibers higher for airborne fibers compared with the bulk product.

Occupational exposure may occur in manufacturing facilities and as well as for end-users, such as during installation, removal, fabrication, or otherwise working with glass wool outside the manufacturing environment (end-use). OSHA has estimated that more than 225,000 workers in the United States are exposed to synthetic mineral fibers in manufacturing and end-use applications. General population exposure may occur from exposure to SVFs from insulation and building materials or from fibers in the air near manufacturing facilities or areas near building fires or implosions. Exposure may also occur during do-it-yourself home remodeling activities.

No traditional biological indices of exposure exist for SVFs, although the measurement of fibers in human lung tissue has been attempted as a means to assess exposure to SVFs. In addition, a recent study investigated the use of nasal lavage as a biomonitoring method for SVFs.

Fine mineral fiber emissions are regulated by the EPA, respirable fibers ("particulates not otherwise regulated") are regulated by OSHA; ACGIH, NIOSH, and OSHA have set guidelines for fibers in the air in the workplace.

3 Human Cancer Studies

This review examines the evidence for the carcinogenicity of glass wool in human populations. The potential carcinogenicity of glass wool has been investigated in a substantial number of cohort and case-control studies. Most of the cohort studies have been mortality studies; few incidence studies have been conducted. The largest studies were conducted on workers involved in the manufacture of SVF. These include (1) combined cohort mortality studies of U.S. workers conducted by the University of Pittsburgh, which comprised a total of nearly 26,700 workers potentially exposed to glass wool at the last follow-up (Marsh *et al.* 2001c, Marsh *et al.* 2001b, Marsh *et al.* 2001a, Stone *et al.* 2004), together with nested case-control studies of this cohort (Chiazze *et al.* 1992, Chiazze *et al.* 1993, Enterline *et al.* 1987, Marsh *et al.* 2001a, Stone *et al.* 2001, Youk *et al.* 2001); (2) a European cohort mortality study comprising a total of 6,936 glass wool-exposed workers with at least 1 year of employment at the last follow-up (Boffetta *et al.* 1997), an incidence study of 2,611 workers from this cohort (Boffetta *et al.* 1999) and a nested case-control study of part of this cohort (Gardner *et al.* 1988); (3) a smaller Canadian cohort studied by Shannon *et al.* (2005, 1984, 1987); and (4) a smaller hospital-based French cohort studied by Moulin *et al.* (1986). Other cohort studies have been conducted of workers exposed to glass wool during use, mainly through employment in insulation work in the construction industry.

Section 3.1 describes cohort and case-control studies of manufacturing workers who were exposed mostly to glass wool, rather than to mixed fibers including rock or slag wool, glass filament, or special fibers. Section 3.2 describes findings for workers exposed mostly to mixed glass wool and glass filament. In Section 3.3, two mortality and/or incidence cohort studies and a series of mainly population-based, case-control studies of potential mixed SVF exposure are briefly reviewed. In these studies, glass wool exposure may have occurred but was not sufficiently characterized by the investigators to enable a quantitative or qualitative assessment of potential exposure to glass wool to be made. In the case-control studies (except those nested within cohort studies) it is usually not possible to identify the exact source of the potential exposure to glass wool among cases or controls.

3.1 Glass wool exposure: cohort and case-control studies

Data from the groups in these studies who were exposed mostly to glass wool are reported in Table 3-4. Studies of other unclassified or mixed SVF are reported as Tables 3-5 and 3-6.

3.1.1 U.S. cohort

A number of U.S. plants (Table 3-1) manufacturing one or other SVF have been studied by various investigators from the 1980's onwards, both as separate cohorts and, under the direction of the University of Pittsburgh, as a combined cohort. Parts of this cohort were previously studied and followed up by Enterline and colleagues (Bayliss *et al.* 1976, Enterline and Henderson 1975, Enterline and Marsh 1980, 1984, Enterline *et al.* 1983, Enterline *et al.* 1987, Marsh *et al.* 1990, Morgan *et al.* 1981), including nested case-control studies of respiratory cancers by Enterline *et al.* (1987), and Chiazze *et al.* (1992, 1993, see Section 3.1.1.3).

The cohort (Table 3-4), including production and maintenance workers from 8 plants in 7 states that produced glass wool or glass wool and filament, comprising white male workers only, was followed up initially until 1977 and then 1982 (Enterline and Marsh 1984, Enterline *et al.* 1983, Enterline *et al.* 1987), and subsequently to 1985 (Marsh *et al.* 1990). The cohort was then expanded to include nonwhite and women workers and followed until 1992 (Marsh *et al.* 2001c, Marsh *et al.* 2001b, Marsh *et al.* 2001a, Stone *et al.* 2004). The most recent follow-up also included a second nested case-control study, a more detailed characterization of work histories and exposures, and an examination of the effect of smoking and other co-exposures. No significant increase in respiratory cancer mortality was observed among glass wool-exposed workers either in the cohort SMR analysis or in the nested case-control study before or after controlling for smoking in the 1982 follow-up (Enterline *et al.* 1987). In the 1985 follow-up (Marsh *et al.* 1990), 340 deaths from respiratory cancer were observed among a total of 11,380 workers (SMR = 1.12 [95% CI = 1.00 to 1.24, according to IARC (2002)]; a trend towards an increase in risk with increasing time since first employment was observed but not with duration of employment.

U.S. cohort study: 1992 update (Marsh et al. 2001a)

In the 1992 follow-up, five of the plants produced mostly glass wool with a small amount of continuous glass filament production, and 4 plants (two of which were combined as Plant 15) produced a mixture of glass wool and continuous filament. Four of the eight plants also made small diameter (< 1.5 μm) glass or quartz microfibers for special applications as well as larger glass wool fibers and/or filament (Table 3-4).

Table 3-1. Plants making glass wool or glass wool + filament in the United States (University of Pittsburgh Study)

Plant No.	Location	Principal Type of SVF	Total Person-Years of Job-Location-Weighted Exposure to Respirable Fibers (1992 update)
1	Parkersburg, WV	Mostly wool[a]	11,276
4	Kansas City, KS	Mostly wool	31,337
6	Santa Clara, CA	Mostly wool[a]	17,868
11	Defiance, OH	Mostly wool	21,927
14	Shelbyville, IN	Mostly wool	9,532
9	Newark, OH	Wool + filament[a]	85,379
10	Waterville, OH	Wool + filament[a]	11,433
15	Kansas City, KS	Wool + filament	31,942

Source of data: Marsh *et al.* 2001a.

[a]Special-application glass or quartz microfibers (< 1.5 μm) were also made at these plant

In this follow-up female workers and male workers employed between 1963 and 1978 were included to make a total of 32,110 workers, of whom 26,679 were exposed to glass wool or glass wool and filament. 12.5% of the entire cohort (including glass wool, wool and filament, and filament workers) was female, representing 9.5% of the person-years of employment. In this follow-up, approximately half the cohort had > 5 years of employment. Most of the male workers were engaged in production. Short-term workers (< 1 year or, in two plants, < 6 months) were excluded. Approximately half of the cohort had > 30 years from first employment to the last ascertainment of vital status, 80% of the cohort > 20, and nearly all workers had > 10 years. Death certificates were obtained for 98.2% of deaths in the first follow-up and 98.8% in the second. Standardized mortality ratios (SMRs) were calculated for white males and females from both local (county) rates and U.S. population rates. The cohort study had 80% statistical power to detect a 10% or greater excess risk of respiratory cancer, although the power is less for the female workers when analyzed separately.

Detailed exposure matrices were constructed from a combination of historical technological data and industrial hygiene data, collected from 1970 to 1990, to estimate plant, job title and department-specific exposures and individual worker job histories. The air contaminants produced by the major production processes in glass fiber production facilities include the fibers themselves and other emissions associated with various processes (Quinn *et al.* 2001, Smith *et al.* 2001) (see Table 2-5). Smith and coworkers used airborne fiber data contained in manufacturer databases to assign respirable fiber exposures to workers in the cohort study. Estimated fiberglass exposures to small-diameter fibers measured before 1980 ranged from 0.027 to 1.94 fibers/cm^3 with a mean of 0.662 fibers/cm^3. Estimated exposure levels measured after 1980 were very similar, ranging from 0.025 to 1.86 fibers/cm^3 with a mean of 0.745 fibers/cm^3.

For the nested case-control study and internal analyses of female workers (discussed below), mean, median, and cumulative exposures to respirable fibers (Rfib) (defined as fibers with diameter less than or equal to 3 μm, length greater than 5 μm, aspect ratio greater than 3:1) and a range of other compounds were estimated from plant start-up to the end of 1987 (or closure if before this date) (Quinn *et al.* 2001, Smith *et al.* 2001,

Stone *et al.* 1996). The median average exposure to Rfib in the 5 glass wool plants ranged from 0.039 to 0.167 fibers/cm^3 and the median cumulative exposure ranged from 1.839 to 6.382 fibers/cm^3-months. In the 3 glass wool + filament plants the median average exposure ranged from 0.018 to 0.040 fibers/ cm^3 and the median cumulative exposure from 0.892–1.833 fibers/cm^3-months. No distinction was made between respirable fibers from glass wool and from filament. It is important to note, however, that respirable fiber concentrations in filament operations were often up to three orders of magnitude lower than glass wool fibers and frequently at or below the limit of detection. Thus the estimated Rfib levels essentially reflect glass wool exposure. Smith *et al.* (2001) also identified co-exposures to substances that met the following criteria: (1) they are widely used, (2) there is a reasonable likelihood of exposure, (3) they have been used for more than 10 years, and (4) there must be a possible cancer risk, particularly lung cancer. Based on these criteria, the authors identified the following co-exposures in the synthetic vitreous fiber industry: aromatic hydrocarbons, arsenic, asbestos, asphalt, crystalline silica, epoxide compounds, formaldehyde, phenol (as a possible promoter), polycyclic aromatic hydrocarbons, radioactivity, styrene, and urea (as a possible promoter).

With respect to respiratory cancers, Marsh *et al*. reported statistical results for combined respiratory system cancers (larynx, trachea, bronchus and lung, ICD 160-163), and for other cancers. A total of 838 deaths from lung cancer were reported for the entire cohort, together with 29 deaths from cancer of the larynx and 7 other respiratory system cancers. Among the combined (male and female) cohort, a slight excess of respiratory cancer was observed among all workers in glass wool plants but not in glass wool + filament or filament-only plants. A small, but significant excess of respiratory cancers was observed among workers exposed to glass wool with 1 to 5 years employment. No excess of respiratory cancers was observed among long-term (> 5 years employment) workers for either glass wool, glass wool + filament, or filament-only plants (Table 3-2). According to calculations made by IARC (2002), the SMR for respiratory cancer for all 8 plants was [1.06, 95% CI = 0.99 to 1.14, 733 deaths)] using county rates for comparison (U.S. rates were slightly lower). For the four plants making special fibers, the SMR calculated by IARC (2002) was [1.06, 95% CI = 0.97 to 1.15, 490 deaths)]. Among all workers in the 10 fiberglass plants in this study (including those making filament only, which comprised

approximately 17% of the total cohort), a slight trend towards increasing respiratory cancer mortality with time since first employment and calendar time was observed but not with duration of employment. Workers in the whole cohort hired between 1950 and 1959 had slightly higher rates for respiratory cancers than those hired before or after that period [data not shown]. No consistent relationship with age at hire was observed among the whole cohort [data not shown].

Table 3-2. Respiratory (larynx and lung) cancers in the United States (University of Pittsburgh cohort–1992 follow-up (males and females combined)

Plants	Principal fiber type	Respiratory cancer cases/exposed workers, 1992 update	SMR (95% CI)[c] (all workers)[d]	SMR (95% CI)[c] (workers with ≥ 5 years employment)[d]
1[a],4,6[a],11,14	Mostly glass wool[b]	243/10,961	1.18 (1.04–1.34)	1.06 (0.90–1.26)
9[a,e],10[a,e],15[e]	Glass wool and filament	490/15,718	1.02 (0.94–1.12)	1.03 (0.91–1.16)
2,5	Filament	141/5431	1.04 (0.87–1.22)	0.96 (0.76–1.19)

Source: Adapted from data in Marsh *et al.* 2001a. 32,110 male and female workers with > 1 year employment (except for one glass wool and one glass wool + filament plant where workers with > 6 months emplyment were included) (1945 to 1978) followed up to 1992 with 98.8% ascertainment of cause of death.

[a] Special application fibers also made (< 1.5 μm diameter). Note that SMRs for these plants were, with the exception of Plant 6, slightly lower those for the combined glass wool and/or filament producing plants. [Plant 1: 35 deaths; SMR = 1.04 (95% CI = 0.72–1.45); Plant 6: 54 deaths; SMR = 1.28 (95% CI = 0.96–1.67); Plant 9: 374 deaths; SMR = 1.05 (95% CI = 0.94–1.16; Plant 10: 27 deaths; SMR = 0.85 (95% CI = 0.56–1.24); data for all workers.]

[b]Includes some filament operations.

[c]Compared with local county rates. The use of local county mortality rates to calculate SMRs results in slightly lower estimated risk compared with national rates.

[d]In the whole cohort, including filament workers, there were 15,404 short-term workers (< 5 years employment) and 16,706 long-term workers (≥ 5 years employment).

[e]Separate facilities or buildings used for making either wool or filament.

With respect to other cancers, an analysis of mortality due to mesothelioma among the entire 10-plant cohort was conducted (Marsh *et al.* 2001b), but was complicated by the lack of consistent diagnostic identification by ICD codes, particularly in older versions, according to the authors. Using different classification schemes to identify "possible" malignant mesothelioma deaths, 10 such cases were initially identified via death certificates in the entire cohort (16 plants, including 6 other plants with rock/slag wool production). Eigth of ten possible deaths had potential asbestos exposure, according to the authors. Pathology reports for 5 of these deaths revealed that 2 were not

mesothelioma and 3 were doubtful. No excess of mesothelioma was found in the glass wool cohort using a broad definition of mesothelioma spanning several ICD revisions or a more strict definition that focused on pleural mesothelioma.

No other cancers were found in significant excess; nonsignificant excesses of buccal cavity and pharynx cancers (SMR = 1.11, 95% CI = 0.85 to 1.42, 63 deaths) and bladder and other urinary organs cancers (SMR = 1.07, 95% CI = 0.82 to 1.37, 64 deaths, county comparisons) were observed among the entire glass wool and filament cohort (10 plants) (Marsh *et al.* 2001a). The SMR for all 2,243 cancer deaths combined was 0.94 (95% CI = 0.90 to 0.98; county comparison) in the total fiber-exposed cohort, [which suggests the possibility of a healthy worker effect].

Smoking is the major potential confounder for respiratory system cancers. An early attempt to adjust for the effect of smoking on respiratory cancer mortality for the male Newark, Ohio workers in the U.S. cohort was conducted by Chiazze *et al.* (1995), based on smoking data obtained from interviews with proxies or survivors with a 13% sample of the original Newark cohort (used in a subsequent case-control analysis; see below). The estimated smoking prevalence thus obtained was compared with expected smoking rates for white males obtained from several National Heath Interview Surveys. According to this method, some 82% of the cohort were estimated to have ever smoked compared with an expected 73%; when SMRs were adjusted for smoking, they decreased (in the Newark cohort followed to 1982) from 119.6 to 107.8 (range 105.4 to 110.2 for minimum and maximum smoking estimates). A somewhat higher prevalence of ever-smokers was observed among male fiberglass workers compared with the 1980 U.S. population. (Some 76% had ever smoked and most had started before the age of 20.) Rates were also higher than among local populations. A slightly lower than expected rate of ever smoking was observed among the sample of female smokers (41.8% vs. 44.5% in the U.S. population). No relationship between smoking and level of glass wool exposure was observed. Adjustment for estimated smoking reduced all respiratory cancer SMRs to non-significance (Marsh *et al.* 2001c), and the authors estimated that approximately 7% of the observed excess of respiratory cancers in males could be attributable to smoking. (Note that the effect of smoking on respiratory cancer risk was also examined in a nested

case-control study of this cohort, described below, together with the effects of other potential exposures, such as formaldehyde. No attempt to adjust for formaldehyde or other exposures was made in the external analysis of mortality in this cohort, however.)

U.S. cohort study: detailed mortality study of female workers (Stone et al. *2004)*

Stone *et al.* (2004) conducted a more detailed mortality study of the 266 cancer deaths, including 53 deaths from respiratory cancers, observed among the 4,008 women in the 1992 follow-up. The women were employed from 1945 to 1978 (the period of 1940 to 1978 was used for one plant) with at least one year of employment (6 months was used as the minimum for 2 plants). Less than 2% were lost to follow-up. Only 633 (15.8%) of the women worked in the five glass wool plants and the majority of these worked in packing, transport, or inspection rather than production. 1,765 (44.0%) worked in the wool and filament plants and 1,610 (40.2%) in filament plants. The median average level and median cumulative level of exposure to respirable fibers in glass wool plants was 0.059 fibers/cm^3 and 2.951 fibers/cm^3-months respectively and 0.008 fibers/cm^3 and 0.318 fibers/cm^3-months respectively in the plants making a combination of glass wool and filament. Filament exposures were very low, with an average median of 0.001 fibers/cm^3 and cumulative exposure of 0.079 fibers/cm^3-month. These are somewhat lower exposures than those experienced by the male cohort. A large number of the female workers had minimal exposure (close to the limits of detection) and less than 5 years of employment. SMRs were presented for the whole SVF cohort only (including filament-only workers).

With respect to respiratory cancers excluding the larynx, the observed SMR was 0.99 (95% CI = 0.74 to 1.29, 52 deaths) compared with national rates and 1.02 (95% CI = 0.76 to 1.34) compared with county rates (Stone *et al.* 2004). One death from cancer of the larynx was observed (SMR = 0.98, 95% CI = 0.02 to 5.48, county comparison). No other excess cancer deaths were observed. In an internal analysis, respiratory cancers among women who were potentially exposed to mostly glass wool were compared with women potentially exposed to filament only. Only the 3,563 women who were alive and at risk at 44 years of age (the age at death of the youngest respiratory cancer case) were included. All respiratory cancer mortality (ICD 160–163) was significantly elevated among mostly

glass wool-exposed workers in a univariate analysis (relative risk (RR) = 3.24, 95% CI = 1.27 to 8.28, 6 deaths). In a multivariate model including average and cumulative exposure and time since first employment, the estimated RR increased to 3.69 (95% CI = 1.38 to 9.87) when glass wool-exposed women were compared with filament only-exposed women. Neither the average level nor cumulative level of Rfib exposure were related to respiratory cancer mortality in the entire cohort. In contrast with the male workers, the risk of respiratory cancer was significantly associated with duration of employment (Wald *P* value = 0.020): women with between 5 and 9 years employment had a significantly elevated relative risk of 2.30 (95% CI = 1.24 to 4.27, 16 deaths) on univariate analysis compared to workers with less than 5 years employment, but not with 10 or more years of employment. (Note that the number of cases in the latter group was small.) Time since first employment was associated with an increased risk of respiratory cancers (Wald *P* value = 0.037), particularly for workers with over 30 years since first employment relative to those with < 20 years since first employment. Women hired between 1950 and 170 had higher rates of respiratory cancer than those hired before 1950 or after 1970 (Wald *P* value = 0.042). Multivariate analyses confirmed the patterns seen in the univariate analysis. No significant effects of other exposures were observed in this cohort; cumulative exposure to formaldehyde was examined in both univariate and multivariate analyses but was not significantly associated with glass wool exposure or respiratory cancers.

With respect to other cancers among the entire female cohort (Stone *et al.* 2004), no excess mortality of other cancer sites was observed, although a nonsignificantly elevated risk of cancer of the bladder and other urinary organs was observed in the entire cohort (SMR = 1.62, 95% CI 0.70 to 3.20, 8 deaths, local comparison). Deaths from several specific cancers (breast, and lymphatic and hematopoietic cancers) occurred significantly less often than in the comparison populations. The SMR for all 266 cancer deaths was 0.77 (95% CI = 0.68 to 0.87, county comparison) in this cohort, [which suggests the possibility of a healthy worker effect as in the male cohort].

Case-control studies

Enterline *et al.* (1987) conducted a nested case-control study of workers who had died from respiratory cancers between 1950 and 1982 from the first follow-up of the U.S. cohort from 1977 to 1982. The case-control study included all 333 cases or deaths from respiratory cancers occurring from 1950 to 1982 among workers exposed to glass wool and continuous filament. A random sample of 529 workers without malignant respiratory cancer or nonmalignant respiratory disease, 43 or more years of age and stratified by age of birth and plant were selected as controls, representing about 4% of the cohort. Smoking data were obtained from interviews with surviving cases and controls or proxies. All cases and controls used in the analyses had data either on ever-smoking status (242 cases and 387 controls) and/or duration and time since starting smoking (211 cases and 374 controls). In maximum likelihood stepwise logistic regression models, smoking was, as expected, significantly related to respiratory cancers. Cumulative exposure to glass wool was not significantly associated with respiratory cancer risk before or after controlling for different measures of smoking, nor was there evidence of an interaction effect between smoking and cumulative exposure to glass wool among these cases. Note that among 34- to 44-year-old referents (representing 5% of the referents) and 65+ year olds (representing 24% of the referents) a somewhat greater percentage were estimated to have ever smoked than in the U.S. white male population (75% vs. 71.2% for 34 to 44 year olds vs. U.S. white male population and 73.4% and 66.7% for 65+ year olds vs. U.S. white male population). Among the 45 to 64 year olds, representing 71% of the referents, the proportion of ever smokers was similar to that of the U.S. population (79.2% vs. 78.4%, respectively).

Chiazze *et al.* (1992, 1993) conducted a nested case-control study of the Newark, Ohio cohort (Plant 9), employed for one year or more from 1940 to 1962 and followed until 1982. Exposure and work histories were reconstructed from employment, plant process, and industrial hygiene records. In addition to glass wool and filament, exposures were estimated for asbestos, talc, formaldehyde, respirable silica, and asphalt. In an initial analysis of 162 cases of lung cancer and 363 controls, unadjusted odds ratios for cumulative respirable glass wool exposure (using workers exposed to < 100 fibers/cm^3-days as a reference) were 1.43 (95% CI = 0.90 to 2.72, 37 cases) for 100 to 299.9

fibers/cm^3-days and 0.95 (95% CI = 0.56 to 1.61, 27 cases) for > 300 fibers/cm^3-days (Chiazze *et al.* 1993). Only year of hire before 1945 and employment duration of less than 5 years were significantly associated with an increase in lung cancer in the unadjusted analysis. Demographic and smoking data were obtained by interview, mainly with proxy respondents, for approximately 87% of cases and 79% of controls. Among subjects for whom interview data were available were 152 deaths from respiratory cancers, including 144 lung cancer deaths, which were matched with 276 respiratory cancer and 260 lung cancer controls, respectively, all from within the plant. In a conditional logistic regression model, which also simultaneously adjusted for smoking, education, age at first hire, year of hire, asbestos, formaldehyde, silica, talc, and asphalt, odds ratios for lung cancer were significantly associated only with smoking (6+ months vs. less than 6 months) and age at first hire, and nonsignificantly elevated with year of hire before 1945 (Chiazze *et al.* 1993). In this model, nonsignificant odds ratios of 1.72 (95% CI = 0.77 to 3.87) for cumulative exposure of 100 to 299.99 fibers/cm^3-days and 0.58 (95% CI = 0.20 to 1.71) for cumulative exposure of 300 or greater fibers/cm^3-days were observed in comparison with lung cancers among workers with exposure to <100 fibers/cm^3-days. Ever smoking (6 months or more) yielded an adjusted odds ratio of 26.17 (95% CI = 3.32 to 206.5) for lung cancer. [No actual industrial hygiene records existed for the period of employment of the cohort, and a number of changes in industrial process took place over the years, according to the authors, who relied on a historical reconstruction of exposures to characterize workers' exposure profiles (Chiazze *et al.* 1993). Smoking and other demographic data were obtained from proxies, and 14% of respiratory cancer cases and 22% of their controls who did not have interview data were excluded. A large majority of the cohort smoked (57% to 96%, depending on the decade of birth, for occasional + regular smokers) and nearly all the lung cancer cases occurred among smokers.]

A nested case-control study was also conducted of male workers who had died of respiratory cancers between 1970 and 1992, from the later (1992) follow-up of the entire cohort (Marsh *et al.* 2001a, Stone *et al.* 2001, Youk *et al.* 2001). Approximately 40% of the workers had < 5 years employment. Adjustment for smoking was possible for 631 cases and 570 randomly selected age-matched controls at risk during the 1970 to 1992

time period and who were alive at the time the age-matched case died. Data on smoking was obtained by interviews with proxies of the cases and either proxies of the respondents or the respondents themselves. Subjects were classified as ever or never smokers: 609 cases were ever smokers and 22 cases were never smokers. In the unadjusted analysis, Rfib exposure was associated with a nonsignificantly elevated risk of respiratory cancers (RR = 1.79, 95% CI = 0.77 to 4.14, 622 exposed, 9 unexposed cases, $P = 0.17$). After adjustment for ever smoking, the relative risk was slightly decreased (RR = 1.37, 95% CI = 0.55 to 3.42, $P = 0.50$). For respiratory cancers among workers in the five mostly glass wool plants, the unadjusted relative risk of respiratory cancers (compared with 92 cases among workers in filament-only plants) was 1.12 (95% CI = 0.77 to 1.62, 183 cases); this risk decreased slightly after adjustment for ever smoking (RR = 1.06, 95% CI = 0.71 to 1.60). For workers exposed to both glass wool and filament, the adjusted relative risk was 1.01 (95% CI = 0.69 to 1.47, 356 cases). No association with duration of employment or time since first employment was observed in either unadjusted or adjusted analyses. [Note that race was a significant risk factor for respiratory cancers but was not included in further analyses because most of the excess risk was associated with unknown race.]

Marsh *et al.* also evaluated several measures of exposure to respirable fibers (average, cumulative, and duration) and respiratory cancer risk. Relative risks were calculated for deciles of each exposure measure. Respiratory cancer risk was associated with non-baseline levels of average intensity of exposure to respirable fibers in the unadjusted model ($P = 0.02$), but was not significant after controlling for smoking ($P = 0.07$) or plant and smoking ($P = 0.19$). Several of the exposure decile-specific RRs were significant in the models after controlling for smoking or for smoking and plant. No association was observed between respiratory cancer risk and cumulative exposure to respirable fibers or duration of exposure, and none of the tests for trend was significant.

The association between average intensity of exposure to respirable fibers and respiratory cancers was reanalyzed by different models in two later publications (Stone *et al.* 2001, Youk *et al.* 2001). Youk *et al*. performed analyses using weighted exposure estimates. These included time lags (where exposure is discounted for a specified period before the

start of the observation time) and unlagged or lagged time windows (so that only exposures occurring within certain time frames are counted). Adjusting for smoking, risk estimates for deciles of exposure measures for both average intensity and cumulative exposure to respirable fibers were lower in the weighted models compared with the unweighted models; no relationship between increasing average or cumulative exposure to respirable fibers and respiratory cancer was observed.

Stone *et al.* (2001) performed analyses that allowed the modeling of collinearity, effect modification and potential confounding by co-exposures, including quantitative estimates of formaldehyde and silica exposure and qualitative estimates of other exposures, as well as the effects of smoking and demographic variables. No association was observed between average intensity, cumulative exposure or duration of exposure to respirable fibers and respiratory cancers in numerous polynomial models that included quantitative measures of exposure to respirable fibers, formaldehyde, and silica as continuous variables in the same model.

Ever smoking accounted for some of the heterogeneity in risk among the different plants, according to the authors, suggesting a possible correlation between smoking and exposure to fiber type. Stone *et al.* (2001) reported that nonsmokers had somewhat lower average intensity of exposure and cumulative exposure to respirable fibers than smokers, but there was also no evidence of an interaction effect between smoking and average respirable fiber exposure ($P = 0.60$) (Stone *et al.* 2001).

As noted, a number of other potential exposures (arsenic, asbestos, asphalt, epoxy, formaldehyde, polycyclic aromatic hydrocarbons, phenolics, silica, styrene, and urea) were examined in association with respiratory cancer risk in the case-control study, although with the exception of formaldehyde and silica, only qualitative (exposed or non-exposed) estimates of exposure were available. Using dichotomous variables for each of the co-exposures and adjusting for ever smoking, Marsh *et al.* (2001a) reported a positive significant association for formaldehyde and an inverse significant association for epoxy exposure. In a further analysis using estimates of glass fiber, formaldehyde, and crystalline silica exposure as continuous rather than dichotomous variables (Stone *et al.*

2001), higher levels of formaldehyde exposure were significantly associated with respiratory cancer risk before and after adjustment for smoking. A trend towards increasing risk with the higher silica-exposed group was also observed. Misclassification of exposure to at least some of the co-exposures was considered likely, in part due to the short duration of employment of approximately 40% of the workers in the case-control study (Stone *et al.* 2001).

Strengths and limitations

[The combined male and female U.S. cohort (Marsh *et al.* 2001a) represents close to one million person years at risk and has 80% statistical power to detect a 10% or greater excess risk of respiratory cancer, although the female cohort study of Stone *et al.* (2004) had considerably less power. Ascertainment of vital status was almost complete and the length of follow-up adequate for most expected latency periods. Most of the male workers were engaged in production, and reconstruction of exposures was detailed and based in part on industrial hygiene samples. The major limitations include qualitative rather than quantitative assessments of levels of several potentially confounding co-exposures and limited smoking data, which were obtained mainly from proxies and which did not permit detailed analyses by level or duration of smoking. In addition, approximately 40% of the cohort was short-term workers (less than 5 years employment) and had higher rates of respiratory cancers, but analyses of cancers among these workers by demographic, smoking and occupational co-exposures were not analyzed separately.]

3.1.2 European cohort

IARC has conducted cancer mortality and incidence studies of SVF-exposed male and female production workers in 13 SVF plants across 7 European countries since 1976 (Boffetta *et al.* 1999, Boffetta *et al.* 1997, Boffetta *et al.* 1992, Gardner *et al.* 1988, Gardner *et al.* 1986, Saracci *et al.* 1984, Simonato *et al.* 1986). 8,335 workers, representing 201,105 person-years at risk, were exposed to glass wool from 5 factories, one in each of five countries, and were included in a cohort mortality follow-up by Boffetta *et al.* (1997) (Table 3-3). The U.K. plant, which constituted the largest subcohort and 70% of expected deaths, also produced some continuous filament and other specialty fibers of varying diameter (Gardner *et al.* 1988, Gardner *et al.* 1986). In addition, a

cancer incidence study was conducted of workers in 3 of the 5 countries (excluding the United Kingdom and Italy, which did not have national cancer registries) by Simonato *et al.* (1986). The latter cohort was also followed up in an incidence study by Boffetta *et al.* (1999).

Table 3-3: Plants and workers exposed to glass wool in the European cohort study (Boffetta *et al.* 1997)

Country	No. of workers	Average exposure (fibers/ml)
United Kingdom	4,145	0.01 to 0.16
Sweden	2,022	0.01 to 1.00
Finland	924	0.01 to 0.05
Norway	644	0.01 to 0.07
Italy	600	No information
TOTAL	8,335	

Cherrie *et al.* (1986) conducted exposure measurements for 4 of the glass fiber plants included in the European cohort and reported a range for respirable concentrations of fibers from 0.01 to 1 fibers/cm^3, with the highest concentrations being associated with the manufacture of special fine fiber earplugs. The mean concentrations in main production ranged from 0.01 to 0.05 fibers/cm^3 and in secondary production from 0.02 to 1.00 fibers/cm^3, and are closely comparable to the ranges seen in main and secondary production in the U.S. manufacturing plants. With respect to individual plants, the ranges for average concentrations of respirable fibers across all job categories were 0.01 to 1.00 fibers/ml (Sweden), 0.01 to 0.05 (Finland), 0.01 to 0.07 fibers/cm^3 (Norway) and 0.01 to 0.16 fibers/cm^3 (United Kingdom). The plant in Italy produced glass wool from 1946 to 1960 only, and no contemporary measurements of glass wool were available.

Individual cohorts

Parts of the European cohort have been studied by individual investigators in the component countries. In an early study of part of the Norwegian cohort (Andersen and Langmark 1986), 1 plant producing glass wool was included, but comprised only 23% (N = 546) of their total cohort, the remainder being exposed to rock wool. Cancer mortality

and incidence were reported mainly for both exposed groups combined. A slight excess of all cancer deaths was observed. A significant excess cancer incidence of the buccal cavity and pharynx (SIR = 1.68, 7 cases), and nonsignificantly elevated risks of cancers of the intestine (SIR = 1.24, 17 cases), trachea, bronchus, or lung (SIR = 1.39, 20 cases), and bladder (SIR = 1.20, 8 cases) were reported in the whole cohort [CIs were not specified]. Workers with > 1 year of employment and greater than 20 years since first exposure had a two-fold increase in the risk of lung cancer (SIR = 2.06, 9 cases). Among the glass wool workers, lung cancer incidence was reported separately and was lower than expected (2 cases among those with > 1 year of employment, SIR = 0.69; SIR = 0.63 for the 2 cases among all glass wool workers).

Bertazzi *et al.* (1986) conducted an early study of cancer mortality in a manufacturing plant in Italy, which became part of the European cohort. This plant produced mostly glass wool for about 15 years, until 1960, and then only continuous filament. No asbestos use was reported. 1,098 male workers with greater than 1 year of employment hired up to 10 years prior to the end of follow-up were included. 98.9% were successfully followed up for the period from 1944 to 1983. A slight excess of total cancer deaths was observed compared with national referents; a statistically nonsignificant increase in laryngeal cancer was observed (SMR = 1.88, 95% CI = 0.52 to 4.88, 4 deaths, compared with regional comparison rates). This increase occurred mainly among workers hired prior to 1960 before age 25 and who had at least 15 years since first employment and the greatest cumulative exposure. No significant increases in lung or other cancers were observed (SMR = 0.96 (95% CI = 0.50 to 1.68, 12 lung cancer deaths, compared with regional rates).

In an earlier mortality and incidence study of the Swedish cohort (Plato *et al.* 1995b), male and female glass wool manufacturing workers were included (N = 1970). Mortality was followed from 1952 to 1990 and cancer incidence from 1958 to 1989. No smoking data were available in this study. No excess of mortality from all cancers combined was observed when compared with either regional or national rates (SMR = 1.00, 95% CI = 0.82 to 1.22, 102 deaths; regional comparison). No excess of lung cancers was observed (SMR = 0.97, 95% CI = 0.57 to 1.69, 14 deaths, regional comparison), except for a

nonsignificant excess among workers with 30 or more years since first employment (SMR = 1.43, 95% CI = 0.74 to 3.05, 8 deaths, regional comparison). No significant excesses of other cancers occurred. A similar pattern was observed with lung cancer incidence (SIR = 0.93 (95% CI = 0.54 to 1.48, 17 cases, regional comparison).

In an earlier mortality study of the U.K. glass wool and filament manufacturing workers (Gardner *et al.* 1986), 4,766 male and female workers were followed in a glass wool manufacturing plant from 1946 until 1984. Some asbestos exposure also occurred in this cohort. A slight but nonsignificant excess of lung cancers was observed among males (SMR = 1.24, 95% CI = 0.98 to 1.59, 69 deaths) but not females (SMR = 0.96, 95% CI = 0.60 to 3.09, 7 deaths) when local comparison rates were used. A significant excess of stomach cancer occurred among women workers (SMR = 153, 95% CI = 1.02 to 6.04, 6 deaths, local rates).

The Finnish cohort of glass wool manufacturing workers was studied by Teppo and Kojonen (1986). Some asbestos exposure in addition to glass wool exposure occurred in the plant. Among 616 male and 325 female workers, employed from 1953 to 1977 and followed for an average of 12.1 years to 1981, a slight but nonsignificant excess of all cancers combined was observed among female workers (SMR = 1.16, CI not specified; 12 deaths), and a deficit among male workers (SMR = 0.74, CI not specified; 11 deaths). A slight decrease in lung cancer deaths was observed. A similar pattern was observed for cancer incidence among both sexes combined, with no observed excess of lung cancer (SIR = 0.61, 95% CI = 0.17 to 1.56, 4 cases). Only bone cancer was significantly increased (SIR = 10.26, 95% CI = 1.24 to 37.05, 2 cases). [The study had limited power to detect an effect of glass wool due to the small number of exposed subjects and short follow-up time.]

Combined cohort studies

The combined cohort, consisting of the glass wool cohorts from 5 countries described above, was followed up for mortality until 1990 or 1992, depending on the subcohort (Boffetta *et al.* 1997), and for incidence until 1995 (Boffetta *et al.* 1999). A nested case-control study was also conducted. Loss to follow-up was between approximately 2% and

10%. Exposure was considered in three technological phases (early, intermediate, and late) representing the highest to lowest relative exposure periods (Boffetta *et al.* 1997).

Mortality study. With respect to respiratory cancers, an excess of lung cancer deaths (SMR = 1.27, 95% CI = 1.07 to 1.50, 140 deaths) was observed among 6,936 glass wool workers with at least 1 year of employment and representing 167,675 person-years at risk (Boffetta *et al.* 1997). [It should also be noted that in the total cohort, the SMR for lung cancer was slightly higher among short-term workers with less than 1 year of employment (SMR = 1.48, 95% CI = 1.18 to 1.83, 83 deaths) than longer term workers; short-term workers were not considered further in subsequent analyses, however.] Adjustment of SMRs for local factors reduced the SMR to 1.12 (95% CI = 0.95 to 1.31). 78% of the observed lung cancer deaths occurred in the U.K. cohort, in which the SMR was significantly elevated (SMR (national rates) = 1.37, 95% CI = 1.13 to 1.65, 109 deaths). None of the other 4 glass wool plants had a significant excess of lung cancers, although the number of deaths was low and confidence intervals were wide. Analysis by technological phase (early, intermediate and late) did not suggest a consistent trend in lung cancer mortality (Table 3-4) and no association with duration of employment or time since first employment was observed. With respect to other cancers, a significant increase in all cancer deaths combined was observed among glass wool workers (SMR = 1.11, 95% CI = 1.01 to 1.22, 460 deaths). Some, mostly statistically nonsignificant increases in specific cancers were observed. Buccal cavity and pharyngeal cancer (SMR = 1.47, 95% CI = 0.71 to 2.71, 10 deaths) showed a slight excess in glass wool workers, as did bone cancer (SMR = 2.66. 95% CI = 0.86 to 6.21, 5 deaths), bladder cancer (SMR = 1.13, 95% CI = 0.62 to 1.89, 14 deaths), lymphatic and hematopoietic cancers (SMR = 1.42, 95% CI = 0.94 to 2.07, 27 deaths) and cancers of ill-defined and unspecified sites (SMR = 1.69, 95% CI = 1.13 to 2.42, 29 deaths). One death from mesothelioma among the glass wool cohort was reported.

Incidence study. In the cancer incidence study of 2,611 glass wool workers with greater than 1 year of employment, representing 68,523 person-years at risk were studied (Boffetta *et al.* 1999). Loss to follow-up was approximately 6% for the whole cohort. A nonsignificant excess risk of lung cancer was observed (SIR = 1.28, 95% CI = 0.91 to

1.74, 40 cases). A slight trend towards increased lung cancer risk was observed with increasing time since first employment (> 30 years vs. < 30 years), in contrast to the combined mortality study and findings for the U.K. and Italian cohorts. No relationship between SIR and duration of employment or technological phase was observed (Table 3-4). As in the mortality study, a statistically nonsignificant increase in the SIR for combined oral cavity, pharynx, and larynx cancers was observed (SIR = 1.41, 95% CI = 0.80 to 2.28, 16 cases). SIRs in excess of 1.00 were observed for stomach, breast and bladder cancer, melanoma, leukemia, and ill-defined sites, but none was statistically significant. The observed incidence of all cancers combined was slightly lower than the expected rate (SIR = 0.99, 95% CI = 0.89 to 1.11, 324 cases).

Strengths and limitations. [The size of the combined cohort and time to follow-up yielded sufficient person-years at risk for adequate statistical power and sufficient time since first hire to observe long latency cancers such as lung cancer. Ascertainment of vital status was almost complete. The major limitations were, first, the imprecision of exposure classification within the plants. No work history information was available for the early years of the study (pre-1977), and exposure assessment was confined to the assignment of technological phases within plants. No direct exposure measurements were used in either the SMR or SIR analyses. In addition, no information on potentially confounding exposures, including smoking or other co-exposures, was available.]

Case-control study

A nested case-control study of lung cancers was conducted on 3,548 male and 1,186 female workers at the U.K. glass wool plant, which also produced superfine fibers (1 to 3 μm and 2 to 5 μm diameter) for part of the time (Gardner *et al.* 1988). Up to 8 sex- and age-matched controls from the workforce with greater than 1 year of employment who were alive at the time of death of the case were randomly selected. Based on information about manufacturing processes and job title or category, potential exposure to different types of SVF and asbestos was assigned to cases and controls. No direct measurements of glass fiber levels were available, except for those taken during a survey conducted in 1977 (as part of the cohort study). No data on smoking and other exposures were available. Seventy-three (73) deaths from lung cancer (66 males and 7 females) and 506

controls were included in the final analysis. The relative risk for lung cancer for all respirable superfine and other glass wool fibers (defined as diameter less than or equal to 3 μm, length greater than 5 μm, and aspect ratio greater than 3:1) was 1.2 (95% CI = 0.7 to 2.0, 33 exposed deaths). (For glass wool separately, the relative risk for lung cancer was 1.1 (95% CI = 0.7 to 1.9, 31 deaths) and for superfine fibers separately it was 1.3 (95% CI = 0.3 to 5.8, 2 deaths.) Within individual categories of glass wool fiber types, no statistically significant increases in lung cancer risk were observed. No relationship between duration of exposure, time since first exposure or job category and lung cancer was observed, with the exception of a significant relative risk (RR = 2.0) for 17 lung cancer deaths observed among workers exposed to glass wool and/or superfine fibers with 10 to 19 years since first exposure (CI not stated). No significant association between lung cancer and asbestos was observed, and addition of asbestos exposure to the regression models did not alter the relative risk estimates for glass wool. [The power of the study was not stated but the number of deaths among the different categories of fibers was small; too few workers were exposed to superfine fibers, in particular, for conclusions to be drawn, according to the authors. In addition, only 48% of the original cohort had five or more years of employment. It is not clear whether the length of time since first exposure (not stated) was adequate to detect long-latency cancers for a number of the workers.]

3.1.3 Canadian cohort

This cohort mortality study included 2,557 male workers employed in glass wool manufacture for at least 90 days from 1955 to 1977. The first follow-up study was conducted in 1984 (Shannon *et al.* 1984, Shannon *et al.* 1987) and the second study extended the follow-up from 1984 to the end of 1997 and included data on cancer incidence from 1969 to 1997 (Shannon *et al.* 2005). Findings from the latest follow-up are discussed below.

The cohort consisted of 2,576 men employed for at least 90 days from 1955 to 1977 in three groups followed to 1997: those who worked only in the manufacturing plant, those who worked only in the office, and those who worked in both ("mixed exposure") (Shannon *et al.* 2005, Shannon *et al.* 1984, Shannon *et al.* 1987). No direct measurements

of exposure were available prior to 1978; samples taken subsequently suggested average levels below 0.1 fibers/cm^3 and peaks generally less than 0.2 fibers/cm^3. Average concentrations between 1977 and 1990 were approximately 0.03 fibers/cm^3 (Shannon *et al.* 2005). It is not clear what proportion of these fibers were in the respirable range. Ascertainment of vital status was complete for 97% of the cohort, but only 502 workers were followed beyond 20 years after first exposure, 13 of whom were office workers [with little opportunity for exposure]. No smoking data were available.

A total of 94 deaths from all cancers combined were observed among the manufacturing plant workers (SMR = 1.15, 95% CI = 0.93 to 1.40); 12 among office workers (SMR = 1.13, 95% CI = 0.59 to 1.98) and 6 among workers with mixed (plant and office) exposure (SMR = 0.47, 95% CI = 0.17 to 1.03) (Shannon *et al.* 2005). All subsequent analyses were of plant-only workers.

With respect to respiratory cancers, a significant excess of lung cancer was observed among plant-only workers (SMR = 1.63, 95% CI = 1.18 to 2.21, 42 deaths, $P < 0.05$). Among plant-only workers with greater than 20 years of employment, the SMR for lung cancer was 1.89 (95% CI = 1.10 to 3.03, 17 deaths, $P < 0.05$) and for plant-only workers with > 20 years of employment and >40 years since date of first exposure, the SMR for lung cancer was 2.82 (95% CI = 1.13 to 5.82, 7 deaths, $P < 0.05$). For plant-only workers employed prior to 1960, lung cancer mortality was also significantly elevated (SMR = 1.72, CI not stated, 31 deaths, $P < 0.05$). No other trends with duration of employment or date since first exposure were significant. When only lung cancer deaths since the end of the first follow-up among plant-only workers were considered, 23 additional deaths were observed. While this number was higher than expected (expected = 16.2) the SMR was not significant (1.42, 95% CI = 0.90 to 2.13).

In the cancer incidence part of the study, comparing rates with cancer registry data for Ontario (available only from 1969), 50 cases of lung cancer were observed among plant-only workers from 1969 to 1996, yielding a significant SIR of 1.60 (95% CI = 1.19 to 2.11, $P < 0.05$). 54 cases of lung cancer were observed among all workers combined (SIR = 1.34, 95% CI = 1.01 to 1.75, $P < 0.05$). SIRs in excess of 1 were also observed for

kidney, rectal, and stomach cancer, but none was significant. No significant trends with duration of employment or date since first exposure were observed, although, as in the case of lung cancer mortality, the highest SIR occurred among the group with the longest duration of employment, according to the authors (SIRs not reported). While comparison with province-based cancer mortality and incidence data were considered less than ideal, the authors noted that local (county) rates were too unstable to permit comparison.

The authors concluded that, notwithstanding the lack of direct exposure data and lack of smoking data, there was a suggestion of a modest effect of glass wool on lung cancer rates in both the mortality and morbidity data. The authors also considered that the lack of an increase in mortality or morbidity from known non-cancer, smoking-related diseases such as cardiovascular and respiratory disease suggested that smoking among exposed workers was not excessive.

With respect to other cancers in the extended mortality study, no significantly elevated cancers were observed among plant workers, although kidney cancer rates were somewhat higher than expected (SMR = 1.46, 95% CI = 0.30 to 4.27, 3 deaths). In the cancer incidence study, a statistically significant excess of kidney cancer was observed in the whole cohort (SIR = 1.92, 95% CI = 1.05 to 3.21, 14 cases, P <0.05) but did not reach significance among the plant-only workers (SIR = 1.92, 95% CI = 0.96 to 3.43, 11 cases). The authors concluded that glass wool is unlikely to be a causal factor in kidney cancer, in part because no other cohort study has observed such an effect. They suggested that silica might be a factor, since it is associated with renal disease, although as noted, no direct measurements of silica or other agents were available for this cohort. [It should also be noted that the overall all-cause SMR in this cohort was low (0.88), suggesting a healthy worker effect.]

3.1.4 French cohort

A small cohort incidence study, initiated as a result of an observed "excess" of cancers of the pharynx, larynx, and buccal cavity by an industrial physician, was conducted on male workers in a single glass wool plant in France (Moulin *et al.* 1986). All 1,374 male workers employed between 1975 and 1984 with a minimum of 1 year of employment were studied. Follow-up was conducted up to the time of study (1984), so that the

maximum length of follow-up was approximately 10 years. Approximately 12,800 person-years at risk were available for analysis, of which slightly more than half were among potentially exposed production workers. 101 men lost to follow-up were considered to be still living and contributed 465 person-years to exposure. Twenty-five percent of the whole cohort were followed for more than 20 years since first hire, and the average duration of employment was 16 years. Cancers were identified from company insurance records and regional cancer rates were used for comparison. The mean diameter of fibers in the plant was 6.4 μm, with 30% <3 μm and 10% < 1 μm. The average concentration of respirable fibers was <0.2 fibers/cm^3. Smoking data were collected for 966 men still working at the factory in 1983 and estimated for the remainder of the cohort. Forty-one cases of cancer were reported over the total of ten years of follow-up. Five cases of lung cancer were observed in the whole cohort (SIR = 0.74, 95% CI = 0.24 to 1.72). Referent cancer rates used for the estimation of standardized incidence ratios were calculated based on the average of three regional cancer registries in France, weighted by population size. (Although none of the referent population rates included the region in which the plant was located, mortality rates for the plant region were similar to those for the regions in which incidence data were available, according to the authors.)

Among potentially exposed production workers, there were 4 cases of lung cancer, too few to permit an adequate examination of a trend by duration of employment (Table 3-4). An increase in cancers of the upper respiratory tract or upper gastrointestinal tract combined (ICD 8th Revision codes 141 to 149 and 161) was observed, which included cancer of the larynx, buccal cavity, and pharynx (SIR = 2.18, 95% CI = 1.31 to 3.41, 19 cases in the entire cohort) and 17 among potentially exposed production workers). Among the production workers with greater than 10 years duration of employment, a significantly increase in the risk of these latter cancers was observed (Table 3-4). No other SIRs for specific cancers were reported by the authors, but the SIR for all other cancers combined (excluding lung, upper respiratory and digestive tract cancers) was lower than expected (SIR = 0.77, 95% CI = 0.45 to 1.24, 17 cases), suggesting the possibility of a healthy worker effect. Smoking was not taken into account in the statistical analyses, but the authors noted that the smoking prevalence among the current

employees was similar to population values, with approximately 75% ever-smokers; slightly fewer heavy current smokers than expected were observed.

[The principal limitations of the study include the small numbers of potentially exposed production workers and short follow-up time (10 years), yielding only 12,800 person-years of risk, only approximately half of which occurred among production workers. This limits the power of the study to detect an effect of glass wool, particularly for long-latency cancers. In addition, it is not clear whether the reliance on company insurance records to identify cancer incidence cases may result in the misclassification or omission of certain cases.]

Table 3-4. Retrospective cohort and nested case-control studies for mostly glass wool exposures

Reference Geographical Location	Population, Follow-up, and Methods	Exposure Assessment and Exposure Levels	Effects	Comments
Marsh *et al.* 2001a,b,c United States	*Retrospective cohort mortality study* 32,110 male and female (12.5%), mainly white workers at 10 plants: 5 glass wool (GW) 3 GW and continuous filament plants (GW+F) 2 glass filament plants (F) Employed > 1 year (6 mo 2 plants); 48 % of workers had < 5 years employment Employed: 1945–78 Follow-up: 1946–92 *Person-years (exposed to respirable fibers):* GW: 91,931 GW+F: 220,694 F: 45,796 10 Plants: 266,490 ~98.8% death certificates obtained SMRs based on local rates (SMRs based on national rates were slightly higher)	*Exposure assessment* Exposure matrices based on industrial hygiene measurements and knowledge of past process, and workers job histories *Median plant-level exposures (respirable fibers)* 5 GW plants avg. intensity: 0.039–0.167 f/cm^3 cumulative: 1.839–6.382 f/cm^3-mo 3 GW+F plants avg. intensity: 0.018–0.040 f/cm^3 cumulative: 0.892–1.833 f/cm^3-mo 4 plants also made < 1.5 μm diameter specialty fibers	SMR (95% CI); no. of deaths (local comparison) *Total cohort (10 plants)* all causes 0.90 (0.88–0.92); 8,436 all cancers 0.94 (0.90–0.98); 2,243 *Cancers with non-significant increased SMRs* buccal cavity and pharynx 1.11 (0.85–1.42); 63 urinary bladder and other urinary tumor 1.07 (0.82–1.37); 64 mesothelioma 10 possible deaths (8 GW) *Respiratory cancer (lung + larynx)* Fiber production group GW: 1.18 (1.04–1.34); 243 GW+F: 1.02 (0.94–1.12); 490 F: 1.04 (0.87–1.22); 141 Total cohort all 1. 06 (1.00–1.14); 874 duration < 5 yr 1.12 (1.01–1.24); 378 ≥ 5 yr 1.03 (0.94–1.12); 496 Exposure – response relationships SMRs increased slightly with time since first employment and calendar period of follow-up but not with duration of employment	*Confounding* Adjusting for estimated smoking reduced SMRs to nonsignificance Estimated smoking prevalence from sample of workers suggested slightly higher rates of ever-smokers in males and slightly lower rates in females compared with 1980 U.S. population Exposure to 15 other agents monitored, including formaldehyde (FOR), asbestos, silica 8/10 possible mesothelioma deaths also exposed to asbestos. Inability to correctly identify mesothelioma from death certificates and/or ICD codes; pathology review was available for 5 cases: 2 cases were not mesothelioma and the other 3 were questionable. Two other approaches to coding cause of death

Reference Geographical Location	Population, Follow-up, and Methods	Exposure Assessment and Exposure Levels	Effects	Comments
				suggest no excess risk of mesotheliomas among GW workers
Marsh *et al.* 2001a Stone *et al.* 2001 Youk *et al.* 2001 United States	*Nested case-control study of respiratory cancer (lung and larynx)* Cohort: U.S. cohort established by Marsh *et al.* 2001a Cases: 631 males with smoking information who died from respiratory cancer from 1970–1992 Controls: 570 males, age matched with smoking information, selected randomly from all males at risk from 1970–1992 Relative risks calculated by conditional logistic regression in univariate and multivariate models adjusted for ever-smoking prevalence Summary exposure measures: RRs estimated for deciles of each exposure measure, *P*-values calculated for global test and for trend Marsh *et al.* 2001 –	*Exposure Assessment* Same as Marsh *et al.* above Job location-weighted exposures were determined for a given time period, plant, department, and job title, and were used to determine quantitative exposure to respirable fibers (RFib) Other agents – quantitative exposure estimated for formaldehyde (FOR); qualitative estimation for other agents Summary exposure measures: RFib duration (RFib-dur) RFib cumulative (RFib-cum) RFib average intensity exposure (RFib-AIE)	Adjusted RR (95% CI); no. of deaths for respiratory cancers RFib 1.37 (0.55–3.42); 622 Fiber production group F: 1.0 (Ref); 92 GW: 1.06 (0.71–1.60); 183 GW+F: 1.01 (0.69–1.47); 356 P_{trend} Duration of employment $P > 0.05$ Time since first employment $P > 0.05$ RFib summary exposure measures (Marsh *et al.* 2001a) *P* for Global Test Smoking: Unadjusted Adjusted RFib-dur $P > 0.21$ $P > 0.21$ RFib-cum $P > 0.30$ $P > 0.30$ RFib-AIE $P = 0.02$ $P = 0.07$ (RFib-AIE, $P = 0.19$ when adjusted for smoking and plant). Some statistically significant RR for specific deciles of AIE exposure found in the two adjusted models, None of the test for trends were significant RFib summary exposure measures: Time weighted (Youk *et al.* 2001) or polynomial models (Stone *et al.* 2001) No association with RFib-AIE or RFib-cum	*Confounding* Smoking and race were significantly associated with respiratory cancer risk Smoking information obtained from interviews with proxies and survivors 98% of workers exposed to RFib, 91% to FOR, and 77% to phenolics; other exposures included urea, silica, and asbestos Formaldehyde exposure significantly related to respiratory cancer before and after adjustment for smoking, no association with exposure to other substances Small numbers prevented evaluation of effect modification by smoking

Reference Geographical Location	Population, Follow-up, and Methods	Exposure Assessment and Exposure Levels	Effects	Comments
	adjusted for smoking and smoking and plant Youk *et al.* 2001 – exposure-weighted models (time lags or lagged time windows) Stone *et al.* 2004 – orthogonal polynomial models adjusted for co-exposure to other agents			
Stone *et al.* 2004 United States	*Retrospective cohort mortality study* 4,008 females (mainly white) employed > 1 year (6 mo 2 plants) from the 10 plant cohort established by Marsh (see above for details) No. workers for product GW: 633 (15.8%) GW+F: 1765 F: 1610 98.5% death certificates obtained (10 plants) *Analyses:* External: SMRs based on local rates Internal: respiratory system cancer (N = 53) 3,563 women – alive at or	*Exposure assessment* Same as in Marsh *et al.* above, with the addition of quantitative exposure assessment for respirable fibers (diameter ≤ 3 μm, length greater than 5 μm, aspect ratio > 3:1) and formaldehyde (FOR); qualitative assessment for other exposures *Median exposure levels (respirable fibers)* GW plants: avg. intensity: 0.059 f/cm^3 cumulative: 2.951 f/cm^3-mo GW+F plants: avg. intensity: 0.008 f/cm^3 cumulative: 0.318 f/cm^3-mo F plants: avg. intensity: 0.001 f/cm^3 cumulative: 0.079 f/cm^3-mo Majority of the women had RFib-	SMR (95% CI); no. of deaths (local comparison) *Total cohort (10 plants)* all causes 0.77 (0.72–0.82), 914 all cancers 0.77 (0.68–0.87); 266 *Cancers with increased SMRs and respiratory cancers* urinary bladder and other urinary tumors 1.62 (0.70–3.20); 8 respiratory cancer (trachea, bronchus, lung) 1.02 (0.76–1.34); 52 laryngeal cancer 0.98 (0.02–5.48); 1 Internal analyses (multivariate) for respiratory cancer: RR (95% CI); cases or P_{trend} *Univariate analyses* Fiber production group (P = 0.014) F: 1.0 (ref); 18 GW+F: 1.36 (0.76–2.45); 29 GW: 3.24 (1.27–8.28); 6	*Confounding* Two-thirds of the workers exposed to formaldehyde; correlation between glass fibers r = 0.71 for G+F, and 0.74 for GW+F Smoking information not ascertained *Limitations* Few exposed cases Most women worked < 5 years. Women had lower exposures than male workers

Reference Geographical Location	Population, Follow-up, and Methods	Exposure Assessment and Exposure Levels	Effects	Comments
	beyond > 44 yrs Multivariate regression: Rfib-cum and FOR-cum evaluated in 4 models that also adjusted for fiber production group (FPG) and the following variables identified in univariate analyses: Model 1: FPG only Model 2: FPG + yr of hire Model 3: FPG + employment duration Model 4: FPG + time since first employment Test for interaction between RFib and FOR was performed.	cum exposure less than 20 f/cm^3-mo 90% person-years associated with RFib 5 exposure patterns examined: (1) no RFib (small numbers) (2) RFib no FOR (3) RFib + FOR, no phenolics, no urea (4) RFib + FOR + phenolics, no urea (5) all	Exposure-response, P_{trend} Employment duration 0.020 Year of hire 0.042 Time since first exposure 0.037 $P > 0.05$ for age at hire, exposure pattern and plant RFib-cum (f/cm^3) 1.00 (0.96–1.06); 49 *Multivariate regression* No association with RFib-cum or FoR in any of the four models Similar findings as univariate: $P < 0.05$ for duration of employment (model 3), time since first exposure and FPG (model 4), but $P > 0.05$ for year of hire. Test for interaction (Rfib and FOR) $P > 0.66$	
Chiazze *et al.* 1992 Christensen *et al.* 1993 United States	*Nested case-control study of respiratory cancer* Cohort: glass wool production and maintenance workers at plant 9 from Marsh *et al.* cohort, employed > 1 year, and followed from 1940–82 Cases: 144 confirmed deaths from lung cancer available for matched analyses	*Exposure assessment* Cumulative exposure to GW or GW+F based on employee work history and historical exposure reconstruction	OR (95% CI) for lung cancer *Unadjusted model* Cumulative exposure: (RFib (f/mL) < 100 1.0 (ref); 98 100–299.9 f/cm^3 1.43 (0.90–2.27); 37 ≥ 300 f/cm^3 0.95 (0.56–1.61); 27 Year of hire 1945 or later 1.0 (ref) before 1945 2.18 (1.39–3.42) Employment duration	*Confounding* Lung cancer was significantly associated with smoking but not with exposure to talc, asbestos, silica, asphalt fumes, or total particulates

Reference Geographical Location	Population, Follow-up, and Methods	Exposure Assessment and Exposure Levels	Effects	Comments
	Controls: 260 workers matched for age and survival Unadjusted matched analysis (162 cases and 363 controls); conditional logistic regression analysis examined other exposures, smoking, employment and demographic variables; final model included all significant variables from first step		5 years or more 1.0 (ref) < 5 years 1.11 (076–1.61) *Adjusted model (smoking and demographic variables)* In general ORs slightly lower in adjusted model Never smokers 1.0 (ref) ≥ 6 mo. smokers 26.1 (3.32–206.5)	
Boffetta *et al.* 1997 UK, Norway, Finland, Italy, and Sweden	*Retrospective cohort mortality study* Employed: > 1 year Employed: 1933–77 Follow-up: 1933–90 or 92 6,936 male and female glass wool manufacturing workers in 5 countries (part of larger cohort of SVF workers) Person-years: 167,675 96% follow up SMRs calculated using national rates	*Exposure assessment* Based on work histories Historical exposure investigation. Workers were assigned to three technological phases of production process based on date of first employment: early (assumed highest exposures) intermediate late (assumed lowest exposures)	SMR (95% CI); no. of deaths (national comparison) all causes 1.05 (1.00–1.10); 1,679 all cancers 1.11 (1.01–1.22); 460 *Cancers with increased SMRs* buccal cavity and pharynx 1.47 (0.71–2.71); 10 urinary bladder 1.13 (0.62–1.89); 14 bone 2.66 (0.86–6.21); 5 LH (not leukemia) 1.42 (0.94–2.07); 27 ill-defined sites 1.69 (1.13–2.42); 29 respiratory cancers (trachea, bronchus, and lung) 1.27 (1.07–1.50); 140 laryngeal cancer 1.08 (0.29–2.75); 4 mesothelioma 1 death *Technological phase: lung cancer* early 1.07 (0.64–1.67); 19	*Confounding* The U.K. plant also produced asbestos and superfine fibers; potential exposure to bitumen at another plant. *Other comments* Among rock/slag workers (part of the large SVF cohort), lung and oral cancer were significantly related to time since first employment in internal analyses, but no internal analyses was reported for glass wool workers

Reference Geographical Location	Population, Follow-up, and Methods	Exposure Assessment and Exposure Levels	Effects	Comments
			intermediate 1.40 (1.14–1.70); 100 late 1.02 (0.63–1.56); 21 *Plant (Significant SMRs)* 10 (U.K) 1.37 (1.13–1.65); 109 Workers at all plants with employment > 30 yr had slightly higher SMRs for lung cancer but none significant	
Boffetta *et al.* 1999 Norway, Finland and Sweden	*Retrospective incidence study* 2,611 male and female workers glass wool production workers at 3 plants Employed: > 1 yr Employed: 1933–77 Follow-up: 1933–95 Person-years: 68,523 Follow-up rate: 94.2% SIRs calculated using national rates RR for lung cancer and cancers of the oral cavity, pharynx and larynx were calculated using models that included age, gender, age, country, technological phase, time since first employment and employment duration	*Exposure Assessment* Work histories Workers assigned to 3 technological phases (early, intermediate, and late) as reported above	SIR (95% CI); no. of cases (national comparison) all cancers 0.99 (0.89–1.11); 324 *Cancers with elevated SIR* lung cancer 1.28 (0.91–1.74); 40 oral cavity, pharynx, larynx 1.41 (0.80–2.28); 16 bladder 1.39 (0.88–2.08); 23 breast 1.08 (0.72–1.55); 29 skin melanoma 1.13 (0.54–2.08); 10 leukemia 1.25 (0.54–2.46); 8 mesothelioma no cases Regression analyses: RR (95% CI) no. of cases. P_{trend} *Lung cancer* *Time since first employment* (P_{trend} = 0.2) ≤ 19 yr 1, 10 cases 20–29 yr 1.9 (0.8–4.8); 15 ≥ 30 yr 2.3 (0.6–9.2); 15 *Employment duration (with 15-yr lag) and technological phase*	Subset (3 of 5 factories) of Boffetta *et al.* 1997 cohort Work histories available until 1977 Slight trend towards increase in lung cancer for those with > 30 yr since first employment vs. < 30 yr

Reference Geographical Location	Population, Follow-up, and Methods	Exposure Assessment and Exposure Levels	Effects	Comments
			RR < 1.0, and $P_{trend} > 0.05$ *Oral cavity, pharynx and larynx* *Time since first employment (P_{trend} = 0.03)* ≤ 19 yr 1 (ref); 2 20–29 yr 9.1 (1.6–52.7); 7 ≥ 30 yr 12.2 (1.1–132); 7 *Employment duration (with 15-yr lag) and technological phase* $P_{trend} > 0.05$, no consistent patterns; no cases in intermediate phase	
Gardner *et al.* 1988 UK	*Nested case-control study of lung cancer mortality* Cohort: U.K. plant was part of the Boffetta cohort 3,548 men, 1,186 women Employed > 1 year Employed: 1946–78 Follow-up: 1948–84 Cases: 73 (66 men, 7 women) non-office workers who died from lung cancer Controls: 506 workers randomly chosen and matched by age, gender, and alive at the death of corresponding case (up to 8 controls for each case) RR calculated by conditional logistic	*Exposure Assessment* Factory records (job titles, dates, and clock numbers, type of fiber produced) used to code job descriptions. Workers categorized by fiber type and occupational groups. Superfine (specialty) fibers (1–3 or 2–5 μm diameter) and glass wool fibers produced by flame attenuation process (superfine only), Owens blowing process and rotary TEL process, both of which resulted in respirable fibers (diameter < 3 μm, length > 5 μm and aspect ratio 3:1)	RR (95% CI): cases/controls for lung cancerfor lung cancer *Fiber type* all respirable fibers 1.2 (0.7–2.0); 33 all glasswool 1.1 (0.7–1.9); 31 all superfine fibers 1.3 (0.3–5.8); 2 Higher RR for glass wool produced by Owens (1.4) than TEL process (0.9) *Occupational category* No significant associations observed for most general categories, but lung cancer significantly elevated for granulating/blowing wool workers, maintenance engineer workers, boilermen, and warehouse workers *Employment duration and time since first exposure* No significant associations	*Confounding* Workers also exposed to asbestos OR = 1.5 (0.8–2.5, 24 deaths); controlling for asbestos did not alter results for glass wool or superfine fibers No data on smoking available *Other limitations* Small number of exposed cases in the subgroup analyses

Reference Geographical Location	Population, Follow-up, and Methods	Exposure Assessment and Exposure Levels	Effects	Comments
	regression for matched case-control sets.			
Shannon *et al.* 2005 Ontario, Canada	*Retrospective mortality and incidence study* 2,557 male glass wool manufacturing workers; extended follow-up of Shannon *et al.* cohort Mortality Employed: > 90 days Employed: 1955–77 Follow-up: 1955–97 Person-years: 73,761 96.6% of the cohort was traced Incidence Follow-up: 1969–96 SIRs and SMRs calculated using local (Ontario) and adjusted for age and calendar year	*Exposure Assessment* Work histories and information on production. Historical exposures estimated to be < 1 f/mL *Workers divided into 3 groups:* production plant only (~50%) office-only mixed plant and office Analyses refer to plant workers only Due to the uncertainty of historical exposures, cumulative exposure was not calculated *Exposure measurements taken 1977–90:* Range: 0.01 to 0.32 f/cm^3 Average: 0.03 f/cm^3	Mortality study among plant workers SMR (95% CI); no. of deaths (Ontario comparison) all causes 0.93 (0.83–1.05): 299 all cancers 1.15 (0.93–1.40), 94 *Cancers with elevated SMRs* kidney cancer 1.46 (0.30–4.27); 3 lung cancer 1.63 (1.18–2.21); 42 *Lung cancer (95% CI not reported)* Date of first employment pre-1960 1.72; 31, $P < 0.05$ 1960–1970 1.55, 9, $P > 0.05$ post-1970 1.01; 2, $P > 0.05$ Employment duration (yr) > 20 1.89 (1.10–3.03); 17 > 20 + > 40 yr time since first exposure 2.82 (1.13–5.82) Incidence study among plant workers SIR (95% CI); no. of cases *Cancers with elevated SIRs* lung cancer 1.60 (1.19–2.11); 50 kidney cancer 1.92 (0.96–3.14); 11 rectal cancer 1.01 (0.44–2.0); 8 stomach cancer 1.05 (0.39–2.29); 6 Significant elevated SIRs observed for lung and kidney cancer among all plant and office workers combined	*Confounding* Potential exposure to formaldehyde, phenol, carbon monoxide, solvents, asphalt fumes, total dust, crystalline silica; most exposures were less than current threshold levels No information on smoking *Other comments* Not all cancer rates reported

Reference Geographical Location	Population, Follow-up, and Methods	Exposure Assessment and Exposure Levels	Effects	Comments
Moulin *et al.* 1986 France	*Retrospective cohort incidence study* 1,374 male glass wool manufacturing worker employed > 1 yr Person-years: 12,793 Employed: 1975–84 Follow-up: < 2–10 yr SIRs calculated using regional rates	*Exposure assessment* Workers divided into: production workforce (~ ½) administrative staff maintenance staff Production workforce further divided according to work duration in workplaces contaminated by fibers *Environmental surveys 1981* Average fiber concentrations < 0.2 f/cm^3	SIR (95% CI); no. of cases (regional comparison) *Upper respiratory & alimentary tract cancers (buccal cavity, larynx, pharynx)* all workers 2.18 (1.31–3.41); 19 Production workers: exposure duration[a] 1–9 yr 2.02 (0.41–5.84); 3 10–19 yr 3.04 (1.22–6.27); 7 ≥ 20 yr 3.33 (1.34–6.87); 7 *Lung cancer* all workers 0.74 (0.24–1.72); 5 Production workers: exposure duration 1–9 yr 1.82 (0.22–6.57); 2 10–19 yr 0.63 (0.02–3.48); 1 ≥ 20 yr 0.56 (0.01–3.10); 1 *Other cancers* *All other cancers combined (excluding lung, upper respiratory, and GI cancers)* all workers 0.77 (0.45–1.24); 17 Production workers: employment duration 1–9 yr 1.08 (0.29–2.77); 4 10–19 yr 0.94 (0.31–2.20); 5 ≥ 20 yr 0.73 (0.20–1.86); 4	*Confounding* Smoking data obtained for 966 men still present at the factory, estimated smoking in cohort similar to national population rates *Other limitations* Short follow-up period Small numbers of exposed cases Cases identified from social insurance records

LH – lymphohematopoietic.
[a]Analyses are for exposed production workers.

3.2 Mixed glass wool and continuous filament

3.2.1 U.S. cohort

Taking the data for those workers who had estimated exposure to both glass wool and continuous filament (Marsh *et al.* 2001a), there are no significant SMRs and no clear difference in SMRs between mixed exposed workers and those in "mostly" glass wool production. No differences in SMRs were observed when cancer mortality among workers with mixed (glass wool + filament) exposure was compared with those in the three plants that produced only continuous filament. Respiratory cancers among filament-only exposed workers appear to contribute little to the risk among mixed glass wool- and filament-exposed workers (Table 3-4). [Note that filament exposure in the 3 plants producing both types of fiber appears to be very low, suggesting that, as IARC (2002) pointed out, "mixed exposure" workers can be considered to be exposed mainly to glass wool.]

In the case-control study conducted by Chiazze *et al*. (1992, 1993) of 166 lung cancer deaths among workers from one of the plants in the U.S. cohort (described above), that produced both glass wool and continuous glass filament, a decrease in lung cancer risk with cumulative exposure to respirable fibers of both types combined was observed.

3.2.2 European cohort

It appears that the five glass wool plants included in the European cohort produced mostly glass wool. In the case of the plant in the United Kingdom, continuous filament and other special superfine fibers were also produced (Gardner *et al.* 1986), and it is also possible that some workers from the other plants in the combined cohort also had exposure to filament (or other SVF). Among the U.K. workers, no analyses by fiber type were conducted in the mortality study; as noted above, an overall excess of lung cancer deaths was observed when national but not regional comparison rates were used. [In the subsequent nested case-control study of lung cancer among the U.K. workers (Gardner *et al.* 1988) only one case was observed in association with exposure to continuous filament only, and it is not possible to evaluate the risk of lung cancer associated with mixed glass wool and filament exposure. The relative risk for lung cancer among workers exposed to superfine fibers (2 cases) is higher than for glass wool but not significant (Table 3-4)]

3.3 Mixed SVF exposure (not otherwise specified)

There are several other studies of workers and/or populations that might have been exposed to SVF including glass wool, but where exposure was mixed and/or no data are available to categorize exposure by fiber type. These studies have been reviewed previously by IARC (1988, 2002), and are of interest inasmuch as none of them suggests an increase in respiratory cancers unless concomitant asbestos exposure was suspected. The principal studies are reviewed briefly here. These studies are described in Tables 3-5 and 3-6.

3.3.1 Cohort studies

In a cohort incidence study of 135,035 male construction workers in Sweden exposed to SVF (Engholm *et al.* 1987), all but 11 of whom were followed up until 1982, no excess of lung cancer cases was observed (SIR = 0.91, 95% CI = 0.83 to 1.00, 440 cases). An excess of pleural cancers (SIR = 2.13, 95% CI = 1.35 to 3.20, 23 cases) was observed. Considerable exposure to asbestos might also have occurred among these cases, according to the authors, even though in 21 of these cases, the workers answered no to asbestos exposure on an exposure questionnaire. Reliance on self-reported exposures and smoking data was a limitation of this study, according to the authors. In a nested case-control study of this cohort, in which industrial hygienists estimated average exposures, the relative risk for lung cancer was nonsignificantly elevated among workers estimated to have medium or high SVF exposure but no asbestos exposure (RR = 1.21, 95% CI = 0.60 to 2.47), but significantly elevated among those with substantial exposure only to asbestos (Table 3-5).

Cancer mortality and incidence were investigated in a cohort of 2,807 male workers, 1,068 of whom were classified as potentially exposed to SVF and 397 with unknown exposure, who were employed in 11 plants in the Swedish prefabricated wooden house industry (Gustavsson *et al.* 1992, Plato *et al.* 1997, Plato *et al.* 1995a). Men employed for a minimum of 1 year from the start of SVF use [year not identified in papers] to 1971 were followed from 1968 to 1985. It was not possible to distinguish glass wool from rock wool exposure since both sources of insulation material were used at different periods. The other principal exposure was wood dust. Both the number of deaths from combined

cancers and specific cancers, including lung cancer (SMR = 0.68, 95% CI = 0.37 to 1.13, 14 deaths), were lower than expected, with the exception of stomach cancer, which was significantly increased (SMR = 1.59, 95% CI = 1.00 to 2.41, 22 deaths). No relationship between the estimated level of exposure, duration of employment or time since first employment was observed. The incidence study yielded similar results, with a significant excess only for stomach cancer (SIR = 1.78, 95% CI = 1.15 to 2.63, 25 cases) (Table 3-6).

Table 3-5. Retrospective cohort and nested case-control studies for unspecified SVFs

Reference Geographical location	Population, follow-up, and methods	Exposure	Effects	Comments
Engholm *et al.* 1987 Sweden	*Retrospective mortality and incidence study* 135,026 male construction workers Follow-up: 1971–83 Person-years: 1,403,067 Only 11 workers lost to follow-up Average follow-up 9.4 years Incidence determined by linkage to cancer registries and mortality obtained from national files SIRs and SMRs calculated from national rates	Exposure assessment Mixed SVF + asbestos exposure based on self-reports (based on interview at one or more occupational health service check up between 1971 and 1974) for SVF and asbestos Smoking assessed (never, former, current moderate and current heavy) based on self-reports	*SMR (95% CI); no. of cases* all causes 0.68 (0.66–0.69); 7,356 all cancers 0.84 (0.81–0.88); 2,153 respiratory cancer 0.86 (0.79–0.95); 444 *SIR (95% CI); no. of cases* all cancers 0.94 (0.91–0.97); 3,810 lung cancer 0.91 (0.83–1.00); 440 pleural cancer 2.13 (1.35–3.20); 23 larynx cancer 0.81 (0.60–1.07); 48	*Confounding* Probable confounding by asbestos: 18,025 workers exposed to asbestos and SVF *Limitations* Short follow-up period Some inconsistencies in self-reported exposures and smoking data among workers with more than one questionnaire
Engholm *et al.* 1987 Sweden	*Nested case control study: Lung cancer and pleural mesothehelioma* <u>Cohort:</u> Swedish cohort established by Engholm *et al.* 1987 (above) <u>Cases:</u> 424 lung cancer	Industrial hygenists estimated average intensity of exposure based on job tasks: Category 1: no exposure Categories 2–5: lowest to highest intensity Category 6: not assigned	*RR for lung cancer (95% CI)* SVF 1.12 (0.88–1.41) asbestos 0.93 (0.66–1.31) Similar RRs for SVF and asbestos found in models with both SVF and asbestos <u>Exposure categories</u> 4-5 SVF only 2.12 (0.99–4.54) 4–5 asbestos only 2.55 (0.77–8.28)	Most of the cases and controls were only exposed to SVF (as determined by questionnaire) Poor correlation with self-reported exposure to asbestos and intensity of exposure; correlation was

Reference Geographical location	Population, follow-up, and methods	Exposure	Effects	Comments
	cases and 24 pleural mesothelioma diagnosed after first health check Controls: 5 controls matched per case matched for date of health and age, and alive at diagnosis of case RR calculated by conditional logistic regression and adjusted for smoking and population density		3 SVF only 0.96 (0.41–2.21) 3 asbestos only 4.64 (0.46–46.8) 3–5 SVF only 1.45 (0.80–2.62) 3–5 asbestos only 2.89 (1.02–8.14) 3–5 SVF (adjusted for asbestos) 1.21 (0.60–2.47) RR slightly lower in models with both SVF and asbestos; for exposure category 3, RR for asbestos higher in models not adjusting for smoking RR for pleural mesothelioma highest in asbestos intensity level 2 No association with exposure category level for SVF or asbestos	better for SVF Strong association between exposure to asbestos and SVF Some evidence to suggest that subjects were unaware of their exposures to asbestos (no association was found between self-reported exposure to asbestos and pleural mesothelioma)
Gustavsson *et al.* 1992 Plato *et al.* 1997 Plato *et al.* 1995b Sweden	2,807 male workers at 11 factories making prefabricated wooden houses (1068 exposed to SVF, 1342 workers unexposed to SVF) Employed > 1 year by 12/31/1971 Mortality follow-up: 1969–88 Person-years: 49,527 Incidence follow-up 1969–85 Person years: 43,778 SMR calculated using	*Exposure assessment* Current levels available, past exposure estimated by occupational hygienists SVF (glass wool + rock wool) exposure levels were classified for every work period in the work history for all individuals. Respirable fibers (personal sampling): 0.09–1.9 mg/cm (mean 0.5 mg/cm) 8-hour TWA Exposures divided into 5	SMR (95% CI); no. of deaths *Total cohort* all causes 0.89 (0.82–0.97); 554 all cancer 1.02 (0.85–1.20); 137 lung cancer 0.68 (0.37–1.13); 14 *Cancers with increased SMR* stomach 1.59 (1.00–2.41); 22 liver 1.67 (0.45–4.28); 4 pancreas 1.34 (0.71–2.29); 13 lymphomas 1.63 (0.70–3.22); 8 all lymphohematopoietic 1.05 (0.58–1.72); 15 Exposure response	*Confounding* Smoking data on 73% of cohort; cohort workers may have smoked less than average, and the regionally based rates for mortality do not account for lower smoking rates. May be a small amount of residual negative confounding Workers also exposed to wood dust *Other limitations* Small number of deaths

Reference Geographical location	Population, follow-up, and methods	Exposure	Effects	Comments
	regional rates and SIR using national rates	categories: Category Mean f/cm^3 N 0 no exposure 1,342 1 0.06 215 2 0.09 375 3 0.11 478 9 unknown 397	no increase risk of stomach or lung cancer with increasing latency, employment duration, or exposure category (stomach cancer also elevated in category 1, workers not exposed to SVF) SIR (95% CI); no. of cases all cancers 0.94 (0.82–1.09); 194 lung 0.47 (0.24–0.85); 11 *Cancers with increased SIR* stomach 1.78 (1.15–2.63); 25 liver 1.45 (0.62–2.86); 8 pancreas 1.43 (0.71–2.56); 11 nose/nasal 2.00 (0.03–1,113); 1 melanoma 1.28 (0.51–2.64); 7 other skin 1.23 (0.53–2.43); 8 lymphohematopoietic 1.35 (0.85–2.02); 23	and cases

1 LH = lymphohematopoietic cancer.

3.3.2 Other case-control and cancer registry studies

Several population-based or hospital-based case-control studies have examined SVF and cancer outcomes. Most of the studies were on respiratory cancer, and are described in Table 3-6.

Respiratory cancer

Among 176 cases of lung cancer studied in a population-based case-control study by Kjuus *et al.* (1986), no association between SVF and lung cancer was observed after adjustment for smoking (OR = 1.0, 95% CI = 0.4 to 2.5, 13 exposed cases).

Siemiatycki (1991) conducted a population-based, case-control study from 1979 to 1986 in which the associations between 11 cancer sites and occupational exposures were examined among men in Montreal. Cases were compared with both other cancer controls and population controls. No association between potential exposure to "glass wool" (based on converting job histories to probable exposure by industrial hygienists and chemists) and lung cancer was observed (OR = 1.2, 95% CI = 0.5 to 2.5, 11 exposed cases, compared with population controls), after controlling for age, smoking demographic variables, and other exposures. [Note that odds ratios based on population controls were very similar to those based on other cancer controls.] A subsequent report of this study was described by Pintos *et al.* (2008), together with a second case-control study of lung cancer among males and females 35 to 75 years of age exposed to either SVF (not otherwise classified) or asbestos. This study was conducted between 1996 and 2001 among the same population of Montreal as the earlier study. Data on smoking and demographic variables were obtained by interviews with survivors or, in some cases, proxies. Pintos *et al.* (2008) designated exposures as SVF (not otherwise classified). In their report of the first study, "nonsubstantial" exposure to SVF was associated with a nonsignificant increase in the risk of lung cancer (OR = 1.03, 95 % CI = 0.67 to 1.58, 62 cases, but a nonsignificant decrease in risk for "substantial" exposure was also observed (OR = 0.63, 95% CI = 0.23 to 1.43, 13 cases). In the second study, reporting for males only, the OR for nonsubstantial exposure was 1.16 (95% CI = 0.74 to 1.81, 67 cases), and for substantial exposure, the OR = 1.48, (95% CI = 0.52 to 4.21, 11 cases). All odds ratios were adjusted for smoking, asbestos, and demographic variables. According to the

authors, no interaction between smoking and potential SVF exposure was observed, but the number of never smokers in this population was small.

Martin *et al.* (2000) also conducted a small nested case-control study of lung cancer among a cohort of French male utility workers and reported a decrease in risk among 33 cases (as determined from a company-specific job-exposure matrix) who were potentially exposed to SVF compared with 8 controls (OR = 0.73, 95% CI = 0.32 to 1.7, adjusted for socioeconomic status and asbestos exposure).

Bruske-Hohlfeld *et al.* (2000) and Pohlabeln *et al.* (2000) analyzed pooled data from 2 case-control studies of lung cancer incidence among male workers in a variety of occupations in Germany. Exposure to SVF occurred mainly outside the production industry and among insulation fitters in this cohort, and was estimated on the basis of job descriptions obtained from a questionnaire administered to participants. 304 cases and 170 controls had ever been potentially exposed to SVF. For SVF exposure (not otherwise classified), a significant increase in lung cancer risk was observed; the odds ratio for all workers after adjustment for smoking and asbestos exposure was 1.48 (95% CI = 1.17 to 1.88, 304 cases). Workers with greater than 20 years of exposure had a risk of 1.69 (95% CI = 1.01 to 2.81, 61 cases, adjusted for asbestos and smoking), and those with greater than 30 years of exposure had a risk of 2.03 (95% CI = 1.04 to 3.95, 47 cases, both adjusted for asbestos and smoking). Among insulation fitters who reported using glass or mineral wool only and who did not report asbestos exposure, the odds ratio was nonsignificant (1.56, 95% CI = 0.92 to 2.65, 51 cases, adjusted for smoking).

A case-control mortality study of lung cancer among Russian workers exposed to glass wool and/or other SVF was conducted by Baccarelli *et al.* (2006) using autopsy data. Job-specific exposure data were obtained from monitoring data collected by industrial hygiene centers. 474 male and 66 female cases were matched with 582 controls on age, gender, region, and year of death. Controls with smoking-related diseases were excluded. After adjusting for age, smoking, and location the OR for 10 male cases of glass wool exposure was 1.77 (95% CI = 0.57 to 5.51). For 14 male cases exposed to other SVF (excluding glass wool but including slag wool and ceramic fibers) the OR was 3.34 (95%

CI = 1.18 to 9.45). Adjusting for asbestos exposure (found among 4 subjects with lung cancer), the OR among male workers exposed only to glass wool was 1.56 (95% CI = 0.49 to 5.02, cases not specified); for other SVF, excluding glass wool, the OR was 3.25 (95% CI = 1.16 to 9.11, cases not specified). There were only 2 cases of SVF exposure among women, and no excess risk was observed. Analysis of the data by exposure duration and level and cumulative exposure for workers exposed either to glass wool alone or to all SVF did not reveal any significant trends, although the OR for average intensity of exposure among workers exposed to more than 75% of the maximum allowable concentration (MAC) of glass wool (reported by the authors as 2 mg/cm^3) was higher (OR = 3.61, 95% CI = 0.64 to 20.4) than for workers exposed to less than 75% of the MAC (OR = 0.83, 95% CI = 0.16 to 4.18; both ORs adjusted for smoking, age, and region).

A multi-center case-control incidence study of lung cancer among workers exposed for at least one year to asbestos and/or mixed SVF was conducted by Carel *et al.* (2007) among newly diagnosed workers in Central and Eastern Europe and the United Kingdom. 2,205 male cases were frequency matched with 2,305 controls. Exposure and potential confounders were determined by in-person interviews with the subjects. 49% of the 115 SVF-exposed cases were exposed to glass wool alone, and a further 27% to glass wool and mineral fibers. Data were presented only for mixed SVF exposure, however. After adjustment for age, smoking, regional center, asbestos, and other exposures, the OR for SVF exposure was not significant (OR = 1.23, 95% CI = 0.88 to 1.7, 115 cases). No significant trends with exposure duration, level, or cumulative exposure were observed, and no differences were noted by country of residence.

Marchand *et al.* (2000) conducted a hospital-based, case-control study of cancer incidence of the larynx and hypopharynx in association with SVF and/or asbestos exposure. 296 cases of laryngeal cancer and 201 cases of hypopharyngeal cancer were matched with 295 hospital-based controls who had other types of cancer were included in the analysis. For those ever exposed to “mineral wool” (which could include both glass wool and rock/slag wool), nonsignificant excesses of laryngeal cancer (OR = 1.33, 95% CI = 0.91 to 1.95, 130 cases) and hypopharyngeal cancer (OR = 1.55, 95% CI = 0.99 to

2.41, 99 cases) were observed after adjustment for age, smoking, and alcohol consumption. (Statistically significant increases in laryngeal cancer [OR = 1.51, 95% CI = 1.03 to 2.22, number of cases not specified] and hypopharyngeal cancer [OR = 1.65, 95% CI = 1.05 to 2.58, number of cases not specified] were observed among the mineral wool group (adjusted for smoking, age and alcohol consumption) if a 15-year latency period was used in the exposure calculation.) After adjustment for the effect of asbestos, to which most of the subjects were also exposed, the odds ratios for ever exposure to mineral wool were slightly reduced (OR for laryngeal cancer = 1.23, 95% CI = 0.79 to 1.91, 130 cases; OR for epilarynx = 1.61, 95% CI = 0.85 to 3.04, 51 cases; OR for hypopharynx = 1.51, 95% CI = 0.9 to 2.52, 99 cases). (No other types of fibers were associated with ORs exceeding 1, with the exception of laryngeal cancer in association with microfiber exposure [OR adjusted for smoking, age, and alcohol = 1.28, 95% CI = 0.51 to 3.22, 16 cases].)

Other cancers

In a clinic- and population-based study, Rodelsperger *et al.* (2001) investigated pathologically confirmed mesotheliomas among 137 German men and compared their occupations, 125 of which were determined by interview, with those of 125 age-, sex-, year of birth- and residence-matched controls randomly selected from population registries and also interviewed. Self-reported job histories were used to categorize workers according to exposure to SVF (not otherwise classified) and asbestos and estimate their level of exposure. The authors reported a significant 3-fold increase in risk of mesothelioma among SVF-exposed cases after apparently adjusting for asbestos exposure. [Note that the use of self-reported job histories may have resulted in misclassification of exposure, and there may have been residual confounding due to asbestos in this study.]

A hypothesis-generating case-control study of the Montreal population (see Siemiatycki 1991), using controls with cancers other than lung, rectal, or other digestive system cancers, examined the association between rectal cancer and a range of occupational exposures (Dumas *et al.* 2000). Exposures were assigned for cases and controls by industrial hygienists based on interview data for lifetime occupations. Fourteen cases

with "any" estimated exposure to glass wool had an OR (adjusted for age, education, respondent status, alcohol, and smoking) of 0.9 (95% CI = 0.5 to 1.6); 8 cases with "substantial" estimated exposure to glass wool had an unadjusted OR of 4.3 (95% CI = 1.7 to 11.3) compared with controls with other cancers (except lung and other intestinal cancers). None of the analyses adjusted for other exposures, however.

Goldberg *et al.* (2001) also examined the association between 497 cases of colon cancer and a range of occupational exposures in the same male population, using 1,514 age-matched controls with other cancers and a second group of 533 population-based controls; an OR of 1.9 (95% CI = 0.7 to 5.4, 6 cases, adjusted for age, smoking, and exposure to "selected noncollinear" occupational agents and to nonoccupational risk factors) was observed in association with "substantial" glass wool exposure. [Note that it is not clear whether the analysis included adjustment for asbestos and other specifc exposures, however.]

In a small population-based case-control study in Sweden of 404 cases of non-Hodgkin's lymphoma (NHL) conducted by Hardell and Eriksson (1999), a significantly increased risk of NHL was associated with potential exposure to glass wool as ascertained by questionnaire in a univariate analysis (OR = 1.5, 95% CI = 1.0 to 2.3, 63 cases and 76 controls). [Note that some cases and controls were deceased, and proxies were used for questionnaires.] No trend with increasing exposure was noted. [No other variables were considered, however.]

Vasama-Neuvonen *et al.* (1999) and Weiderpass *et al.* (1999, 2003) conducted cancer registry-based studies of 5,072 cases of ovarian cancer (Vasama-Neuvonen *et al.* 1999), 23,638 cases of breast cancer (Weiderepass *et al.* 1999), and 7,935 cases of gastrointestinal cancer (Weiderpass *et al.* 2003) (diagnosed between 1971 and 1995) in association with occupational exposures among the entire female Finnish working population. A nonsignificant association with SVF (not otherwise classified) (SIR = 1.3, 95% CI = 0.9 to 1.8) was observed for ovarian cancer, after controlling for various demographic and childbirth variables, when occupations with 20% or more people with estimated exposure were compared with those with less than 20% exposed. Among the

breast cancer cases, a significant trend towards increasing incidence with higher estimated exposure levels to SVF was observed; medium to high exposure was associated with a significant increase in incidence (SIR = 1.32, 95% CI = 1.05 to 1.66), and low exposure with an SIR of 1.01 (95% CI = 0.90 to 1.12). However, the excess cancers occurred among building workers who were estimated by the authors to have also had asbestos exposure, which was independently associated with a similar level of risk in this cohort. Relative risks were calculated for women with gastrointestinal cancer designated as having either no, low, or medium/high exposure to occupational agents, including SVF. A significant elevation in risk of stomach cancer was observed among women designated as having low exposure to SVF (RR = 1.23, 95% CI = 1.01 to 1.49, number of cases not specified) (Weiderpass *et al.* 2003). The same relative risk was observed in women with medium to high potential exposure but was not significant. Compared with nonexposed women, the trend was significant ($P = 0.03$).

Table 3-6 Studies (case-control and cancer registry studies) of mixed exposure to SVF

Reference Geographical location	Population, Study Period Methods	Exposure	Effects: OR, RR or SIR[a]	Comments
Lung Cancer				
Kjuus *et al.* 1986 Southeast Norway	*Hospital-based,* 1979–83 Cases: 176 males (< 80 yrs), incident lung cancer, identified at two hospitals Controls: 176 hospital patients, age-matched OR calculated by unconditional logistic regresssion; adjusted for smoking	> 3 years exposure to glass fibers (GF) and rock wool (RW) assessed on occupational titles and questionnaires	OR (95% CI) no. of cases 1.0 (0.4–2.5) 13	Adjusted for smoking Controls excluded patients with COPD but included those with heart, lung and other diseases or other malignant neoplasms.
Siemiatycki 1991 Montreal, Canada	*Population-based,* 1979–85 Cases: 857 males, incident lung cancer Controls:1,360 other cancers 533 population controls OR adjusted for age, smoking, demographic factors and occupational exposures	> 5 years of exposure to glass wool, rock (stone) wool, or slag wool	OR (95% CI) no. of cases, using population controls Glass wool 1.2 (0.5–2.5) 11 Rock and slag wool 1.2 (0.5–2.7) 10	CI = 90% Controls included other cancers (except lung and digestive system) OR compared to cancer controls similar to those for population controls
Pintos *et al.* 2008 Montreal, Canada	*Population-based* Study I. (1979-86) Cases: 857 male (35-70 yr) lung cancer Controls: Other cancers: 1349 Population: 533, matched by age and area of residence Study II. (1996-2001) Cases: 741 males and females (35-75 yr) incident lung cancer Controls: 899, matched by age, gender	Exposure to SVF (glass fibers and wool fibers combined) assessed by questionnaire	OR (95% CI) no. of cases *Study I: (cf. pop. controls)* "nonsubstantial" exposure 1.10 (0.37–3.22) 9 "substantial" exposure 0.63 (0.23–1.43) 13 *Study II (cf. pop. controls) males* "nonsubstantial" exposure 1.16 (0.74–1.81) 67 "substantial" exposure	Adjusted for smoking, asbestos, and demographic variables

Reference Geographical location	Population, Study Period Methods	Exposure	Effects: OR, RR or SIR[a]	Comments
	and area of residence OR calculated by unconditional logistic regression; adjusted for age, ethnicity, SES, smoking, study # and other variables		1.48 (0.52–4.21) 11	
Martin *et al.* 2000 France	*Nested case control,* 1978-89 Utility workers Cases: 310 males, incident lung cancer Controls: 1225, cancer-free and matched by age OR calculated by conditional logistic regresssion; adjusted for socioeconomic status and asbestos exposure	Exposure to SVF based on job exposure matrix (JEM)	OR (95% CI) no. of cases 0.73 (0.32–1.70) 33	
Brüske-Hohlfeld *et al.* 2000 Pohlabeln *et al.* 2000 Germany	*Population-based,* 1988–96 Construction/installation workers (≤75 yrs) Cases: 3,498 males, incident lung cancer Controls: 3,541, age and region matched OR calculated by conditional logistic regresssion; adjusted for smoking	Questionnaire based, occupational histories plus supplementary questionnaire for exposure to SVF Median cumulative exposure (expert ratings): Insulation installers: 0.42 fiber years Electronic fitters: 0.04 fiber years	OR (95% CI) no. of cases Ever-exposed (installers) 1.48 (1.17–1.88) 304 (adjusted for asbestos and smoking) Exposed to SVF only, no asbestos (installers) 1.56 (0.92–2.65) 51 (adjusted for smoking) Ever-exposed (fitters) 1.00 (0.63–1.58) 55 (adjusted for asbestos) SVF-exposed > 20 years 1.69 (1.01–2.81) 61 (adjusted for smoking and asbestos) SVF-exposed >30 years 2.03 (1.04–3.95) 47 (adjusted for	Data pooled from 2 studies Exposure did not distinguish between glass, rock, or slag wool

Reference Geographical location	Population, Study Period Methods	Exposure	Effects: OR, RR or SIR[a]	Comments
			smoking and asbestos)	
Baccarelli *et al.* 2006 Leningrad Province, Russia	1993–98 Lung cancer deaths Cases: 474 males, 66 females Controls: 453 males, 129 females, matched by gender, age, region and year of death OR calculated by unconditional multiple logistic regression; adjusted for age, smoking, region of residence	Exposure assessment (including cumulative exposure scores) for glass wool and other SVFs based on monitoring data obtained by local hygiene centers	OR (95% CI) no. of cases Glass wool 1.77 (0.57–5.51) 10 1.56 (0.49–5.02) 6 (both adjusted for asbestos) Other SVF 3.24 (1.16–9.11) 14 (adjusted for asbestos) SVF >75% max. allowable conc. 3.61 (0.64–20.4) SVF <75% max. allowable conc. 0.83 (0.16–4.18)	Cases and controls identified from autopsy records Controls who died from smoking-related diseases were excluded Only 2 females exposed to SVF
Carel *et al.* 2007 Central and Eastern Europe and the UK (7 countries)	*Population-based,* 1998-2002 Cases: 2205 males (<25 yrs) Controls: 2305 males, age matched OR calculated by unconditional logistic regression; adjusted for age, smoking, occupational exposure, and asbestos	> 1 year exposure to SVF (glass wool, mineral wool fibers) determined by questionnaire	OR (95% CI) no. of cases 1.23 (0.88–-1.71) 115	Approximately half SVF workers estimated to be exposed to glass wool alone
Laryngeal Cancer				
Marchand *et al.* 2000 France	*Hospital-based,* 1989-91 Included in analyses: Cases: 296 males, laryngeal cancer 201 males, hypopharyngeal cancer Controls: 295 males, hospital patients with other (nonrespiratory) cancers OR calculated by unconditional logistic	Exposure to SVF (microfibers, mineral wool, ceramic fibers, glass filaments) determined using a French-population JEM	OR (95% CI) no. of cases Rock/slag/glass wool: 1.33 (0.91–1.95) 130 (larynx) 1.55 (0.99–2.41) 99 (hypopharynx) >15 year time lag: 1.51 (1.03–2.22) (larynx)	ORs adjusted for age, smoking and alcohol Most SVF-exposed workers considered to be exposed to asbestos; adjusting for asbestos reduced ORs slightly

Reference Geographical location	Population, Study Period Methods	Exposure	Effects: OR, RR or SIR[a]	Comments
	regresssion; adjusted for age, smoking, alcohol consumption		1.65 (1.05-2.58) (hypopharynx) Microfibers: 1.28 (0.51–3.22) 16 (larynx) 0.78 (0.26–2.38) 7 (hypopharynx)	
Mesothelioma				
Rödelsperger *et al.* 2001 Hamburg, Germany	*Population-based,* 1988-1991 Cases: 125 males Controls: 125 males, matched by age, gender and region of residence OR calculated by conditional logistic regresssion; adjusted for asbestos	Exposure based on questionnaire information on job history and occupational exposures to SVF (and asbestos and other mineral fibers)	OR (95% CI) no. of cases 3.08 (1.17–8.07) 55	Residual confounding with asbestos possible
Rectal and Colon Cancer				
Dumas *et al.* 2000 Montreal, Canada	*Population-based,* 1979–85 Males (same population as Siemiatycki 1991 above) Cases: 257 rectal cancer Controls: (see comments) Other cancers: 1,295 Population: 533 OR calculated by unconditional logistic regresssion	Glass wool exposure based on occupational questionnaire	OR (95% CI) no. of cases *Rectal cancer* "any" exposure 0.9 (0.5–1.6) 14 (cancer controls; adjusted for lifestyle and demographic factors) "substantial" exposure 4.3 (1.7–11.3) 8 (cancer controls; unadjusted)	Controls with other cancers were drawn from Montreal hospitals and excluded lung and digestive system cancers Population controls were age-stratified and randomly selected
Goldberg *et al.* 2001 Montreal,	*Population-based,* 1979–85 (same population as Siemiatycki 1991) Cases: 497 colon cancer (males 35-70 yrs)	> 5 years exposure to glass fibers and mineral wool fibers, estimated from job histories	OR (95% CI) no. of cases *Colon cancer* "nonsubstantial" exposure (low	OR for mineral fibers same as for glass fibers. [Possible mixed exposures]

Reference Geographical location	Population, Study Period Methods	Exposure	Effects: OR, RR or SIR[a]	Comments
Canada	Controls: Other cancers: 1514 Population: 533 males, age-matched OR calculated by unconditional logistic regresssion, using control subjects with other cancers as referent group; adjusted for age, smoking, occupational and several non-occupational exposures	from job histories Concentration scale: Low (near background) Medium (intermediate) High (handled product in concentrated form) Workweek frequency < 5%, 5–30%, > 30%	frequency) 0.9 (0.4–1.6) 15 "substantial" exposure (medium-high frequency) 2.0 (0.8–5.4) 6	exposures] Other cancer control group excluded lung, peritoneum and other digestive cancers
Gastrointestinal cancer				
Weiderpass *et al.* 2003 Finland	*Population-based*, all women born 1907-1945 Finnish cancer registry cases 1971-1995 Cases: 7935 gastrointestinal cancers (ICD7 codes 150-157) Internal comparisons of low to high exposure	Exposure assessed by national occupational survey and construction of national job exposure matrix	RR (95% CI) no. of cases Significant association with SVF only for stomach cancer: 1.0 (ref. no exposure) 1.23 (1.01–1.49) (low exposure) 1.23 (0.85–1.77 (medium/high exposure) *p* for trend 0.03	Adjusted for job turnover rate
Non-Hodgkin's Lymphoma				

Reference Geographical location	Population, Study Period Methods	Exposure	Effects: OR, RR or SIR[a]	Comments
Hardell and Eriksson 1999 Northern and middle Sweden	*Population-based,* 1987-90 Cases: 404 males (≥ 25 yrs) Controls: 741 males, age-matched OR calculated by conditional logistic regresssion	Glass wool Exposure to pesticides and other agents assessed by questionnaires and telephone interviews	OR (95% CI) no. of cases 1.5 (1.0–2.3) 63	Case and controls include deceased males No adjustment for other variables No trend with increasing estimated exposure
Breast and Ovarian Cancer				
Weiderpass *et al.* 1999 Finland	*Registry-based,* 1971–95 Cases: 23,638 breast cancer SIR adjusted for demographics, childbirth, and other variables	Exposure to SVF assessed using job titles and Finnish JEM Three categories: zero low (below median among job titles with exposure probability > 0) medium/high	SIR (95% CI) Medium/high exposure 1.32 (1.05–1.66) Low exposure 1.01 (0.90–1.12)	Possible asbestos exposure
Vasama-Neuvonen *et al.* 1999 Finland	*Registry-based,* 1971–95 Cases: 5,072 ovarian cancer Comparison between occupations with > 20% potentially exposed vs. < 20% potentially exposed SIR adjusted for demographics, childbirth, and other variables	Exposure to SVF assessed using job titles and Finnish JEM Mean level among exposed = 0.2 f/cm^3	SIR (95% CI) 1.3 (0.9–1.8)	Possible asbestos exposure

[a]OR = odds ratio; RR = risk ratio; SIR = standardized incidence ratio.

3.4 Other reviews

Epidemiological studies of glass wool and other SVF exposure were reviewed by IARC in 1988 and 2002. In 1988 IARC classified glass wool, rock wool and slag wool as possibly carcinogenic to humans (Group 2B). The 2002 IARC working group evaluated each of the cohort and case-control studies of glass wool manufacturing workers and studies of mixed SVF exposure among construction workers and other users that are included in the present background document (with the exception of the more recent update of the U.S. cohort by Stone *et al.* (2004), the most recent update of the Canadian cohort by Shannon *et al.* (2005) and the case-control studies of mixed SVF exposure by Baccarelli *et al.* (2006), Carel *et al.* (2007) and Pintos *et al*. (2008). Based primarily on evidence from the U.S. and European cohort and nested case-control studies, IARC (2002) concluded that that the epidemiological evidence for the carcinogenicity of glass wool was "inadequate" and thus did not permit a conclusion regarding the presence or absence of a causal association.

In addition, WHO reviewed the data for glass wool and other SVF in 2000 (WHO 2000). They pointed to the difficulty of distinguishing the effects of SVF from smoking and other co-exposures on lung cancer rates, and concluded that the epidemiological data available to that date suggested no excesses of lung cancers among production workers exposed to glass wool or glass microfibers and no increases in incidence of mesotheliomas among production workers. (WHO did conclude, however, that at least part of the excess cancers observed among rock/slag wool-exposed workers was attributable to exposure to those fibers.) WHO did not evaluate upper respiratory tract cancers or other cancer sites.

3.5 Summary by tumor site

This section summarizes the findings by cancer sites.

3.5.1 Lung cancer and mesothelioma.

The principal cancer sites of interest have been lung cancer and upper respiratory tract cancers, due mainly to the structural similarity between glass wool, other mineral fibers, and asbestos.

The two largest combined cohort mortality studies in the United States and Europe (Boffetta *et al.* 1997, Marsh *et al.* 2001a), at their latest follow-ups, reported SMRs for respiratory cancer of 1.18 (95% CI = 1.04 to 1.34; lung + larynx) (Boffetta *et al.*) and 1.27 (95% CI = 1.07 to 1.50, lung only) (Marsh *et al.*) (males and females combined). Separate subcohort mortality studies of the U.S. and European cohorts and the incidence studies generally report small elevations of respiratory cancer risk similar to those observed in the later combined follow-up studies. Shannon *et al.* (2005) reported an SMR of 1.63 (95% CI = 1.18 to 2.21) and an SIR of 1.60 (1.19 to 2.11) for lung cancer in their second follow-up of a Canadian cohort of glass wool manufacturing workers, but no smoking data were available. Moulin *et al.* (1986) reported a decreased incidence of respiratory cancer among glass wool manufacturing workers in France (SIR = 0.74, 0.24 to 1.72) based on 5 cases and a short follow-up period.

A modest trend of increasing risk of lung cancer among workers with longer time since first employment (greater than30 years) was noted in the U.S. cohort by Marsh *et al.* (2001a) and among workers with greater than 30 years since first hire in the European cohort (Boffetta *et al.* 1997). With respect to duration of exposure, the U.S. workers with less than 5 years of employment had higher SMRs for respiratory cancer than longer-term workers, although there was no consistent trend towards an increase in respiratory cancer with increasing duration of employment (Marsh *et al.* 2001a). In the European mortality cohort, workers with less than one year of employment had slightly higher rates of lung cancer than those with greater than 1 year of employment (these workers were excluded from further analysis). There was no trend towards an increase in lung cancer risk with duration of employment in the incidence study (Boffetta *et al.* 1999).

In the nested case-control studies of U.S. glass wool manufacturing workers (Chiazze *et al.* 1992, Chiazze *et al.* 1993, Marsh *et al.* 2001a, Stone *et al.* 2001, Youk *et al.* 2001) no significant associations between duration of employment, time since first hire, average intensity of exposure and cumulative exposure to glass wool and lung cancer were observed using various measures of estimated exposure to respirable fibers and controlling for smoking and some co-exposures, although in the unadjusted analysis, significant heterogeneity was observed with average intensity of exposure and respiratory

cancer (Marsh *et al.* 2001a). Similarly, an earlier nested case-control study of U.K. workers (Gardner *et al.* 1988) found no increase in lung cancer risk in association with glass wool exposure, with the exception of a 2-fold increase in risk among workers with 10 to 19 years since first hire, who may also have had exposure to superfine fibers. Lung cancers were significantly elevated in certain specific job categories, however.

There are comparatively few women workers in SVF manufacturing, and few have been studied. It is noteworthy that, in the recent detailed follow-up study of women workers in the U.S. cohort (Stone *et al.* 2004), who were estimated to have lower average exposures to glass wool than male workers, no overall increase in respiratory cancers was observed in comparison with national or local rates. However, a statistically significant 3-fold increase in respiratory cancer was observed when an internal comparison with filament-exposed workers was conducted (although only 6 deaths were observed). This increase was seen among relatively short-term workers but not longer-term workers, [although the small numbers of long-term workers limit the power to detect an effect if present].

Two cohort studies (Engholm *et al.* 1987, Gustavsson *et al.* 1992) and several case-control studies (Baccarelli *et al.* 2006, Brüske-Hohlfeld *et al.* 2000, Carel *et al.* 2007, Kjuus *et al.* 1986, Martin *et al.* 2000, Pintos *et al.* 2008, Pohlabeln *et al.* 2000, Siemiatycki 1991) have investigated lung cancer in association with unclassified or mixed SVF. No significant excesses of lung cancer were observed, with the exception of one study (Brüske-Hohlfeld *et al.* 2000, Pohlabeln *et al.* 2000) in which a significant increase in lung cancer was observed among all workers ever potentially exposed to SVF vs. never exposed (OR = 1.48, 95% CI = 1.17 to 1.88, 304 cases, adjusted for smoking and asbestos) and which was mainly confined to workers with 20 to 30 years and 30 or more years of employment.

Berrigan *et al.* (2002) conducted a meta-analysis of respiratory cancers in the SVF studies including a combined analysis of five cohorts exposed to glass wool (Boffetta *et al.* 1997, Enterline and Henderson 1975, Marsh *et al.* 2001a, Morgan *et al.* 1981, Shannon *et al.* 1987), representing a total of 446 observed deaths from respiratory cancers (370.1 expected). The combined SMR for all 5 cohorts was 1.23 (95% CI = 1.10 to 1.38),

compared with SMRs of 1.08 (0.93 to 1.26) for glass filament and 1.32 (1.15 to 1.52) for rock wool. (Note: some laryngeal cancers were included in this analysis).

With respect to deaths from mesothelioma, Boffetta *et al.* (1997) observed only one death from mesothelioma among glass wool-exposed workers, but the authors did not calculate expected rates for this cancer. Marsh *et al.* (2001c) observed 10 possible deaths (8 among glass wool workers) from mesothelioma based on death certificates, at least 3 of which were found to be incorrect based on pathology reports. A deficit of mesotheliomas was observed among glass wool-exposed workers relative to expected rates, according to the authors. In a smaller cohort study, Engholm *et al.* (1987) reported a significant excess of pleural mesothelioma among male construction workers (SIR = 2.13, 95% CI = 1.35 to 3.20, 23 cases). A number of these cases were associated with occupations with potential exposure to asbestos (e.g., plumbers), according to the authors, although self-reported asbestos exposure was considered to be unreliable in this cohort. It is also not clear to what extent exposure to SVF might have occurred among these cases. An earlier case-control study by Rodelsperger *et al.* (2001) also reported a significant 3-fold increase in risk of mesothelioma after adjustment for asbestos and other potential confounders, but the authors acknowledged the possibility of residual confounding by asbestos in this analysis.

3.5.2 Upper gastrointestinal and upper respiratory cancers (other than lung)

Marsh *et al.* (2001a) reported that the SMRs for laryngeal cancer among all the workers in the whole glass fiber cohort (including filament-exposed workers) was 1.04 (95% CI = 0.70 to 1.5, 29 deaths). A nonsignificant decrease in SMR was observed for "other" respiratory cancer was 0.80 (95 % CI = 0.32 to 1.66, 7 deaths). Boffetta *et al.* (1999, 1997) reported statistically nonsignificant excesses of cancer of the larynx among glass wool-exposed workers, and nonsignificant excesses of cancers of the upper gastrointestinal tract (esophagus, buccal cavity, oral cavity, and/or pharynx) have also been reported in both of these cohorts. Moulin *et al.* (1986) also reported a significant excess of "upper respiratory and alimentary tract" cancers (SMR = 2.18, 95% CI = 1.31 to 3.41), but specific cancer sites were not reported. Marchand *et al.* (2000) reported excesses of laryngeal and hypopharyngeal cancer associated with exposure to "mineral

wool" (consisting of rock/slag wool and glass wool) in a case-control study. [Given the low expected rates of these cancers, the power to detect significant increases in mortality or incidence of these cancer sites and to adjust for potential confounders is limited even in large cohort studies.] In the cohort study of Marsh *et al.* (2001a), adjusting for smoking reduced the risk for laryngeal cancer as well as for lung cancer.

3.5.3 Other cancer sites

Among glass wool-manufacturing workers, a number of elevated risks (SMRs or SIRs above 1.0) for deaths or cases in other cancer sites have been reported among glass wool production workers; these sites included bladder (Andersen and Langmark 1986, Boffetta *et al.* 1999, Boffetta *et al.* 1997, Marsh *et al.* 2001a, Stone *et al.* 2004); stomach (Boffetta *et al.* 1997, Gardner *et al.* 1986); intestine (Andersen and Langmark 1986); rectum (Morgan *et al.* 1981); kidney (Shannon *et al.* 2005); prostate (Morgan et al. 1981); bone (Boffetta *et al.* 1997, Teppo and Kojonen 1986); lymphatic and hematopoietic cancers (Boffetta *et al.* 1997, Morgan *et al.* 1981); ill-defined sites (Boffetta *et al.* 1997), and breast, skin melanoma, and leukemia incidence (Boffetta *et al.* 1999). Among other SVF-exposed workers, significantly increased risks in mortality (SMR = 1.59, 95% CI=1.00 to 2.41, 22 deaths); and incidence (SIR = 1.78, 1.15 to 2.63, 25 cases) of stomach cancer were found among male workers in the Swedish prefabricated wooden house industry. (Small increases in cancer morality or incidence were observed for several other sites, but none was significant (Gustavsson *et al.* 1992)).

In addition, in population-based or registry-based case-control studies of subjects with possible exposure to glass wool or mixed SVF, a marginally significant increase in postmenopausal breast cancer was observed by Weiderpass *et al.* (1999), and a marginally significant increase in stomach cancer among women (Weiderpass *et al.* 2003), and a marginally significant increase in non-Hodgkin's lymphoma by Hardell and Ericksson (1999). A significant increase in rectal cancer was observed among 8 male cases with "substantial" estimated exposure to glass wool in a hypothesis-generating study by Dumas *et al.* (2000). A nonsignificant increase in the risk of ovarian cancer was observed by Vasama-Neuvonen *et al.* (1999) and a nonsignificant increase in colon cancer by Goldberg *et al.* (2001).

3.6 [Methodological Issues][1]

Several methodological considerations are important in interpreting the epidemiology studies.

3.6.1 Statistical power of the studies

The most informative studies are the U.S. and European cohort and nested case-control studies of glass wool production workers. The principal methodological strengths of these cohort and case-control studies are, first, that an adequate number of workers have been followed over a sufficient period of time to detect cancers with both shorter and longer latencies, and they yield a large number of person-years at risk and thus sufficient power to detect modest increases in cancer mortality for all but very rare cancers. Second, ascertainment of vital status was close to complete, with little evidence of systematic bias in follow-up. There are also sufficient cancer outcomes to permit some exposure-response relationships to be examined and some confounding variables to be taken into account in internal comparisons and/or case-control analyses. In addition, the U.S. cohort was expanded to include women and non-white subjects. Other cohort and case-control studies are smaller and have relatively low statistical power to detect effects.

3.6.2 Ascertainment of vital status and diagnoses

Mortality and incidence studies rely on complete and accurate ascertainment of vital status or cancer incidence and accurate diagnoses. Follow-up for the larger cohort studies was almost complete and unlikely to be biased in terms of exposure status within the cohorts. Reliance on reported underlying cause of death from death certificates is known to result in some misdiagnoses and incomplete information, but is likely to be nondifferential and thus would bias findings towards the null. Cancer diagnoses obtained in incidence studies from medical records or cancer registries may be more accurate and complete than death certificate data, although some misdiagnoses and information errors occur. The potential impact of misdiagnosis or misclassification of cancer endpoints is clearly more pronounced for rarer cancers where only a few cases are expected, such as cancer of the larynx or pharynx, than for more common cancers such as lung cancer, or

[1] The title of this section is bracketed to indicate the presence of opinion throughout this section rather than bracketing specific statements.

where the possibility of misdiagnosis without additional (e.g., histopathological) confirmation is greater, such as with mesotheliomas.

3.6.3 Appropriateness of comparison populations and control groups

In the standardized mortality studies of Marsh *et al.* (2001a) and Boffetta *et al.* (1997), both national and regional or local comparison expected rates of lung cancer were used to calculate SMRs. In both studies, slightly higher SMRs were obtained when national rather than local (county) comparison rates were used or adjusted for. (Depending on the mobility and other characteristics of the exposed population, local populations are likely to be more representative of the exposed population, assuming that expected cancer rates are calculated from large enough populations to be robust.)

In the U.S. and French cohorts, SMRs for all cancers combined were slightly lower than expected (in Marsh *et al.* 2001a, for example, all-cause cancer mortality was 0.94 (95% CI = 0.90 to 0.98, county comparison) and in the French cohort of Moulin *et al.* (1986) the cancer incidence rate for cancers other than respiratory and upper gastrointestinal tract was 0.77 (95% CI = 0.45 to 1.24), suggesting the possibility of a healthy worker effect. However, in the European combined cohort (Boffetta *et al.* 1997) the SMR for all cancers among the glass wool workers was slightly elevated (1.11, 95% CI = 1.01 to 1.22), although the SIR was not (0.99, 95% CI = 0.89 to 1.11). In the second follow-up of the Canadian cohort (Shannon *et al.* 1987) the SMR for all cancers was also elevated among plant workers (SMR = 1.15, 95% CI = 0.93 to 1.40), although all-cause SMR among plant workers was slightly decreased compared to expected rates (SMR = 0.93).

3.6.4 Determination of exposure-response relationships

Due to a lack of actual exposure measurements across time and in each job category in most of the cohort studies, the construction of job-exposure matrices was based primarily on limited monitoring data and/or knowledge of industrial processes and industrial hygiene practices, changes in these practices over several decades in some cohorts, and job descriptions. In addition, the biopersistence of glass wool fibers (see Section 5) may obscure delineation of meaningful relationships between, on one hand, duration of exposure, or changes in levels of exposure over time, and cancer risk. In addition, the exclusion of short-term workers with less than one year or six months of employment, as

was done in a number of cohort studies, means that the effect of very short-term exposures was not examined.

Adequate follow-up time, especially for cancers of longer latency, such as lung cancer (which might have an average latency of 20 or more years) is also necessary in order to be able to adequately examine exposure-response relationships for such cancers. In the most recent follow-ups of both the U.S. and European cohorts, relatively large numbers of workers had more than 15 to 30 or more years since first exposure. In several other cohort studies, however, the time since first exposure, at least for parts of the cohorts, may have been insufficient to detect an effect if present.

It is possible that referent occupational groups or populations may also have been exposed to glass wool. The possibility of misclassification of exposure among "exposed" and "unexposed" groups, or cases and controls, can significantly impact the ability to detect modest effects of exposure if present, and would generally tend to bias findings towards the null. In the case of the Stone *et al.* (2004) cohort study, for example, internal controls that were exposed to glass filament were used in one comparison, and may possibly have been also exposed to glass wool. In the nested case-control studies, potentially exposed reference groups may have been used for some comparisons (e.g., in Marsh *et al.* 2001a). In plants where workers may have had several jobs or where their jobs did not involve fixed processes or locations within the plant (e.g., maintenance workers, truck drivers, packers, cleaners, etc.) it may be more difficult to characterize exposure than for fixed process jobs. Exposure may also depend on the extent to which airborne exposure to fibers is controlled and contained. According to exposure reconstruction studies carried out by Marsh, Boffetta, and others, the use of resin binders, improved ventilation, and other control measures from, in most cases, the mid 60s to 70s resulted in lower estimated exposures to production workers in later years, and presumably less ambient contamination in the vicinity of the production areas. However, characterization of early exposures is limited by a lack of documented exposure-monitoring data in these and other cohort and case-control studies.

3.6.5 Potentially confounding exposures

For lung cancer, the most significant confounding exposure is smoking. Boffetta *et al.* (1997), citing a model of lung cancer and smoking proposed by Axelson (1978), estimated that a 20% difference in the proportion of smokers could result in a 30% increase in lung cancer among SVF-exposed workers compared with unexposed referents. Smoking data for workers in the European, French, and Canadian cohorts were not available. In the case of the French cohort, an estimate of smoking prevalence was based on information obtained from 966 workers still employed at the factory; the authors concluded that smoking was similar to that in the general population and reported no association with the SIR for lung cancer. Attempts to estimate the extent of smoking and its relationship to observed lung cancer rates in the U.S. case-control studies were based on interviews with samples of survivors or proxy respondents. The estimated proportion of smokers in this study (Buchanich *et al.* 2001, Marsh *et al.* 2001c, Marsh *et al.* 2001a, Stone *et al.* 2001) was somewhat higher than that of the general population, although the proportion of smokers in the female cohort appears to be slightly lower. Marsh *et al.* (2001c) estimated that approximately 7% of the observed increase in respiratory cancers in the entire cohort could be attributable to smoking, and adjusting for this reduced the SMRs for respiratory cancers to nonsignificance. In the case-control study of this cohort (Marsh *et al.* 2001a, Stone *et al.* 2001), ever smoking accounted for a 13-fold increase in risk of lung cancer compared with never smoking; adjustment for ever smoking slightly lowered the risk for lung cancer attributable to glass wool from RR = 1.12 (95% CI = 0.77 to 1.62) to 1.06 (95% CI = 0.71 to 1.60). Residual confounding could obscure a relationship between glass wool and lung cancer, however. Note, however, that in an earlier case-control study of part of the U.S. cohort (Chiazze *et al.* 1992, 1993), adjusting for smoking and other variables did not appear to decrease the risk of lung cancer associated with moderate levels of respirable fiber exposure, although the risk for higher levels was slightly attenuated.

In a number of cohort and case-control studies, including the U.S. cohort, some workers were exposed not only to glass wool but also to glass (continuous) filament, rock wool or other SVF. In the case of continuous filament, the external (SMR) analysis of the U.S. cohort (Marsh *et al.* 2001a) indicated that filament-only workers had a lower risk that

glass wool-only workers, but a slightly higher risk than that observed among mixed GW+F workers. In the nested case-control study of this cohort, a lower risk was observed among workers exposed to filament than to either glass wool alone or glass wool + filament (see Table 3-2). IARC considered the workers in the wool and filament plants in the U.S. cohort to be largely exposed to glass wool (IARC 2002). Exposure to glass filament in other studies also appears to yield a nonsignificant risk of respiratory cancers; the meta-analysis by Berrigan *et al.* (2002) estimated that the overall respiratory cancer risk from filament exposure is low (RR = 1.08, 95% CI = 0.93 to 1.26), whereas for rock wool, the estimated risk is higher than for glass wool (RR = 1.32, 95% CI = 1.15 to 1.52), although smoking or other confounding exposures may account for some or all of the increase in risk. Exposure to superfine fibers might also be associated with an increase in the risk of respiratory cancer, as suggested, for example, by data from Gardner *et al.* (1988). For mixed glass wool and other SVF exposures, especially if they included rock or slag wool, or superfine fibers, it is not possible to distinguish the contribution of one or other type of fiber to the risk of lung cancer.

Other potentially confounding exposures in the glass wool manufacturing industries include asbestos, asphalt, resins, formaldehyde (used in glass wool binders), polyaromatic hydrocarbons, phenolics, silica, styrene, and urea, according to Marsh *et al.* (2001a). Of these, formaldehyde was the most prevalent exposure in the U.S. study and was independently associated with a significant increase in risk of lung cancer (RR = 1.61, 95% CI = 1.02 to 2.57, adjusted for smoking). Asbestos is a potential concern both in manufacturing and in construction and other industries that use glass wool, where asbestos may have been used in the past. Construction workers and fiber installation workers could also be exposed to asbestos during, for example, remediation work on older buildings. In the U.S. cohort, no effect of asbestos was observed in the nested case-control study (Marsh *et al.* 2001a). Of the 10 possible cases of mesothelioma observed in the whole cohort, most appeared to be associated with asbestos, according to the authors (Marsh *et al.* 2001c). In the Boffetta *et al.* study (1997), 4 deaths from mesothelioma occurred in the last follow-up of the entire cohort, but only one among glass wool workers, and at least 3 were related to asbestos exposure, according to the authors. Silica exposure is also a possible concern for respiratory cancers, but in the U.S. cohort, no

relationship was observed, nor were any other potentially confounding exposures significantly associated with respiratory cancers.

3.7 Summary

A number of epidemiological studies have evaluated the relationship between glass wool exposure and cancer in humans. The studies fall into three main groups: (1) cohort and case-control studies of workers in SVF manufacture; (2) cohort or case-control studies of workers exposed in glass wool applications (e.g., insulators and construction workers); and (3) population-based case-control studies.

Studies within the SVF manufacturing industry have attempted to distinguish between exposure to different types of SVF, and the large cohort and nested case-control studies of workers exposed in plants predominantly engaged in glass wool manufacture are the most informative. [The principal limitations of the glass wool cohort and case-control studies of manufacturing workers include potential misclassification of exposure, particularly for past exposures for which few monitoring data are available, inadequate length of follow-up in some studies for cancers of longer latency, potential confounding by smoking or co-exposure to other chemicals, and possible misdiagnosis or inadequate ascertainment of some cancer outcomes, such as mesothelioma. In contrast, studies of workers in SVF applications (two cohort studies and three case-control studies of respiratory cancer) and the population-based case-control studies or cancer registry studies (cancers of the respiratory and/or gastrointestinal tract, non-Hodgkin's lymphoma, breast, colon, ovary and rectum) have generally been unable to distinguish between types of fibers and are consequently less informative, although intermittent exposures may be higher than observed among manufacturing workers (IARC, 2002). In addition, these studies generally have small numbers of potentially glass wool-exposed subjects and shorter follow-up times than studies of manufacturing workers, and thus limited statistical power to detect long-term effects.]

Cancer mortality or incidence has been studied in four cohorts of manufacturing workers: (1) a combined cohort of male and female U.S. SVF manufacturing workers including five plants making mostly glass wool and three making glass wool and filament (Marsh *et al.* 2001a, Stone *et al.* 2004); (2) a combined cohort of male and female manufacturing

workers in five European glass wool plants (Boffetta *et al.* 1997, 1999); (3) a cohort of male manufacturing workers in Canada (Shannon *et al.* 2005); and (4) a cohort of male manufacturing workers in France (Moulin *et al.* 1986). The cohorts of manufacturing workers in the United States and Europe are the largest studies and have adequate follow-up to detect cancers with longer latencies (220,700 person-years of exposure in the U.S. cohort and approximately 201,000 person-years of exposure in the European cohort). In both cohorts, several earlier studies of subcohorts have been conducted, together with two nested case-control studies of respiratory cancer in the U.S. cohort (Marsh *et al*. 2001a, and Chiazze *et al.* 1992, 1993) and one of lung cancer from part of the European cohort (Gardner *et al*. 1988).

Reconstruction of glass wool exposures indicated that measurable exposure to respirable glass wool fibers occurred among production workers, and that exposure was higher in the earlier periods of operations. However, as IARC (2002) noted, the concentrations of fibers to which production workers were exposed were generally low.

The potential effect of glass wool exposure on lung and upper respiratory tract cancers has been studied most extensively, due to the structural similarity between glass wool, other SVFs, and asbestos. Findings for respiratory cancers and other tumor sites of interest are discussed below.

Respiratory cancers

Significant increases in respiratory cancer mortality were observed among glass wool-exposed workers in unadjusted analyses in U.S. (SMR = 1.18, 95% CI = 1.04 to 1.34, lung + larynx, compared with local rates) (Marsh *et al.* 2001a), European (SMR = 1.27, 95% CI = 1.07 to 1.50, lung only, compared with national rates) (Boffetta *et al.* 1997), and Canadian workers (SMR = 1.63, 95% CI = 1.18 to 2.21, lung only, compared with regional rates) (Shannon *et al.* 2005). Among female workers in the U.S. cohort, no increase in respiratory cancer (trachea, bronchus and lung) was observed in the whole cohort compared with national or local mortality rates, but in an internal analysis of glass wool-only vs. filament only-exposed workers, a significant 3-fold increase in these cancers was observed (RR = 3.24, 95% CI = 1.27 to 8.28) (Stone *et al.* 2004). Excesses

of lung cancer incidence were observed among the European workers (SIR = 1.28, 95% CI = 0.91 to 1.74, compared with national rates) (Boffetta *et al.* 1999) and Canadian workers (SIR =1.60, 95% CI = 1.19 to 2.11, compared to regional rates) (Shannon *et al*. 2005), but not among French workers (SIR = 0.74, 95% CI = 0.24 to 1.72, compared with regional rates) (Moulin *et al.* 1986).

Attempts were made to control for the effects of smoking and other potentially confounding exposures, including asbestos, formaldehyde and silica, in the nested case-control study of the U.S. cohort. Adjusting for ever/never smoking (using data obtained from a sample of proxies) reduced the risk of lung cancer mortality among U.S. glass wool workers to nonsignificance. (Formaldehyde exposure was also independently associated with lung cancer in this cohort, but models for glass wool and lung cancer adjusting for both formaldehyde and smoking were not presented.) The available data on these and other potentially confounding exposures have been insufficient to adequately control for them in the European, Canadian, and French studies.

Several studies evaluated exposure-response relationships. In the U.S. cohort and case-control studies, no clear exposure-response relationships with duration of exposure or cumulative exposure were observed. An association between average intensity of exposure was observed in an unadjusted model but not in models adjusted for smoking or other confounders or in weighted-exposure models (Marsh *et al*. 2001a, Stone *et al*. 2001, Youk *et al*. 2001). There was a modest trend towards increased risk with longer time since first hire in the U.S. but not the European cohort. Similarly, in the nested case-control studies of lung cancer among the U.K. subgroup of the European cohorts, no significant exposure-response relationships with lung cancer were observed, with the exception of a significant increase among glass wool and/or superfine fiber-exposed workers after 10 to 19 years since first hire (Gardner *et al.* 1988). In the Canadian cohort, there was some evidence of a trend towards increased risk with longer duration of employment, time since first hire, and year of hire (Shannon *et al.* 2005).

In the two cohort and three case-control studies of lung cancer among construction and other application workers, and in the population-based, case-control studies of lung

cancer, no significant increases in lung cancer risk were observed. [Glass wool exposure cannot be distinguished from other SVF exposure in these studies, and few attempts to adjust for smoking and other confounders were conducted.]

With respect to mesothelioma, only one death was observed among glass wool-exposed workers in the European cohort (Boffetta *et al.* 1997). Marsh *et al.* (2001b) observed 8 possible deaths from malignant mesothelioma among the glass wool or filament-exposed workers, but a review of pathology reports or medical records, which were available for only four of these cases, showed that at least one of them was a misdiagnosis. When either a broad (including benign tumors) or more strict coding scheme for mesothelioma was used, a deficit of cases was observed among glass wool-exposed workers relative to expected rates, according to the authors. An earlier case-control study by Rödelsperger *et al.* (2001) reported a significant 3-fold increase in risk of mesothelioma after adjustment for asbestos and other potential confounders, and a significant 2-fold increase in pleural mesothelioma incidence was observed among a cohort of construction workers by Engholm *et al.* (1987), but confounding by asbestos may have occurred in these studies.

Upper respiratory cancers

Marsh *et al.* (2001a) did not report these cancers separately for the glass wool-exposed workers, but nonsignificant increases in these cancers were observed in the combined (glass wool- and filament-exposed) cohort. In the European cohort, a nonsignificant increase in oral, pharyngeal, and laryngeal mortality and incidence was observed among glass wool-exposed workers (Boffetta *et al.* 1997, 1999). Moulin *et al.* (1986) reported a significant excess of "upper respiratory and alimentary tract" cancers in the French cohort, and Marchand *et al.* (2000) reported nonsignificant increases in laryngeal and hypopharyngeal cancers in an earlier hospital-based case-control study.

Other cancer sites

No significant excess of other tumors has been reported in the largest cohort mortality or incidence studies of production workers. A number of nonsignificantly elevated risks (SMRs or SIRs above 1.0) for deaths or cases of lymphatic and hematopoietic cancers

(Morgan *et al.* 1981; Boffetta *et al.* 1997), leukemia (Boffetta *et al.* 1999) and cancers of the urinary bladder (Andersen and Langmark, 1986; Boffetta *et al.* 1997, 1999; Marsh *et al.* 2001a, Stone *et al.* 2004); stomach (Boffetta *et al.* 1997, Gardner *et al.* 1986); intestine (Andersen and Langmark, 1986); rectum (Morgan *et al.* 1981); kidney (Shannon *et al.* 2005); prostate (Morgan *et al.* 1981); bone (Teppo and Kojonen, 1986, Boffetta *et al.* 1997); ill-defined sites (Boffetta *et al*. 1997) and breast, and skin (melanoma) (Boffetta *et al.* 1999), have been reported in either earlier studies of subcohorts or in the combined follow-up studies.

In population-based, case-control or registry studies of subjects with possible exposure to glass wool, a marginally significant increase in postmenopausal breast cancer and stomach cancer among Finnish women was observed by Weiderpass *et al.* (1999, 2003 respectively) and a marginally significant increase in non-Hodgkin's lymphoma was observed by Hardell and Ericksson (1999). A significant increase in rectal cancer was observed among eight male cases with "substantial" estimated exposure to glass wool in a hypothesis-generating study by Dumas *et al.* (2000). A nonsignificant increase in the risk of ovarian cancer was observed by Vasama-Neuvonen *et al.* (1999) and a nonsignificant increase in colon cancer by Goldberg *et al.* (2001). [The potential contribution of glass fiber exposure to these cancers cannot be distinguished in these studies.]

4 Studies of Cancer in Experimental Animals

The carcinogenicity of glass wool fibers has been investigated in experimental animals (primarily rats and hamsters) by several routes of administration. Furthermore, published reviews covering several decades of research are available (Bunn *et al.* 1993, Davis 1986, Enterline 1991, Gross 1986, Hesterberg and Chase 1996, Hesterberg and Hart 2001, IARC 1988, 2002, Miller *et al.* 1999a, Pott *et al.* 1989, Roller and Pott 1998, Rossiter and Chase 1995, WHO 1988, 2000). The data and findings from these reviews and other publicly available, peer-reviewed carcinogenicity studies in experimental animals are summarized in this section. Inhalation studies are discussed in Section 4.1, intraperitoneal (i.p.) injection studies are discussed in Section 4.2, and studies that used other routes of administration (i.e., intrathoracic, intratracheal, or intrapleural injection or implantation) are discussed in Section 4.3. Section 4.4 describes studies that evaluated fiber characteristics and tumorigenicity, Section 4.5 provides a brief summary of the IARC evaluatons (IARC (1988, 2002), and Section 4.6 summarizes the information in this section.

This document discusses carcinogenicity data for a wide variety of glass fibers. Some of the studies used fibers derived from commercial products made in the United States or Europe, while some used experimental fibers. Even when commercial products were used, fibers were often size-separated, ball-milled, coated, uncoated, or chemically treated to increase the number of respirable fibers or to examine effects of other fiber properties. In a number of cases, test fibers were identified with generic terms such as fiberglass, glass fibers, borosilicate glass fibers, or glass microfibers. A few studies investigated many different types of SVFs covering a broad range of fiber dimensions and other properties. The general categories and descriptions of glass fibers discussed in this section are provided in Table 4-1. More information on the properties and uses of these glass fibers was provided in Sections 1 and 2.

Table 4-1. Insulation glass wools, including special-purpose and experimental fibers[a]

Category	Fiber description	Comments
Consumer products	CertainTeed B glass Insulsafe II MMVF11 German glass wool Manville 901 MMVF10 MMVF10a Owens Corning	Most all of these products are used in building insulation. MMVF11 represents the respirable fraction derived from CertainTeed B glass and MMVF10 represents the respirable fraction derived from Manville 901. MMVF10a fiberglass has a lower fluorine content than MMVF10 (McConnell *et al.* 1999).
Special-purpose commercial products	Tempstran Code 100/475 JM475 Manville Code 100 JM100 JM104 JM108B JM104/475 JM110 JM112 JMC102 JMC104 MMVF33 JM753 JME-glass microfibers 104E	Many special-purpose fibers are made in a variety of diameters (expressed as Codes). Thus JM100, 104, 112, etc. reflect the relative diameter of the fiber with a smaller number representing a finer diameter. All of the listed products through MMVF33 represent JM475 glass. MMVF33 was derived from a mixture of codes 104, 108B, and 110.
Experimental fibers	A and C fibers B, M, P, and V glass B-01-0.9 B-09-0.6 B-09-2.0 Bayer B1, B2, and B3	In most cases, these designations represent fibers that were engineered to be more soluble and less biopersistant than the typical commercial fibers

[a] This table is not intended to be exhaustive but provides a list of the types of fibers used in the experimental animals studies reviewed in this section.

4.1 Inhalation studies

Doses in inhalation studies are expressed as the concentration (usually in mg/m^3) and/or fiber number. It is generally accepted that fiber number rather than mass is the better measure of dose because equal masses of fibers with different dimensions will have large differences in the number of fibers. Fiber numbers are frequently expressed as the number of WHO fibers (the number of fibers ≥ 5 μm in length, < 3 μm in diameter, and having an aspect ratio of at least 3:1) or the number of fibers > 20 μm in length. The number of WHO fibers is believed to represent the number of respirable fibers while the

number of fibers longer than 20 μm represents fibers that are the most biopersistent (Hesterberg and Hart 2001).

Inhalation studies of fibers present specific challenges. Ideally the system should be capable of generating a consistent cloud of respirable fibers without breaking, grinding, or contaminating the fibers. Exposures may be whole body or nose only. The advantage of nose-only systems is that they allow greater control of exposure levels and provide more uniform dosing. Exposures in most of the earlier studies were whole body while most of the later studies used nose-only systems.

4.1.1 Early studies in rodents

Schepers and Delahant (1955) conducted the first chronic inhalation study of insulation glass wool. Fifty white rats and 100 guinea-pigs were exposed in inhalation chambers to medium-caliber (~6 μm diameter) glass wool (0.14 mg/ft^3 [4.9 mg/m^3]) for up to 20 months. At 20 months, the glass wool was replaced with glass cotton (maximum diameter 3 μm) at 0.03 to 0.07 mg/ft^3 [1.1 to 2.5 mg/m^3] for another 20 months (guinea-pigs) or 4 months (rats). No controls were mentioned. The animals were sacrificed in groups of 3 to 5 at various intervals throughout the study. Seventeen guinea-pigs and 20 rats died before the end of the study. Early deaths in guinea-pigs were due to pneumonia and, in rats, were due to lung inflammation. Bronchitis was observed after 12 months, and bronchial epithelial hyperplasia was reported at 18 months. No tumors were reported, and the author concluded that, unlike asbestos, glass wool was not fibrogenic (i.e., did not cause fibrosis). In a subsequent study, Schepers (1974) exposed 100 guinea-pigs for 44 months and 50 rats for 28 months to aerosols of glass wool (0.15 mg/m^3) and cotton dust (0.03 mg/m^3). Fiber diameters in the aerosol were mostly in the range of about 2 to ≥ 10 μm with 20% ≤ 2 μm. Fiber lengths were mostly in the range of about 5 μm to more than 50 μm with 30% ≤ 5 μm. Non-neoplastic lesions of the bronchial epithelium, peribronchiolar structures, and pulmonary parenchyma were observed in 57 guinea-pigs. No pulmonary lesions were reported in 300 controls. Pulmonary lesions (macrophage accumulation in subpleural alveolar spaces) occurred in 16 rats compared with 2 out of 310 controls. No neoplastic lesions occurred in either species.

Gross *et al.* (1970) studied the pulmonary reactions in rats and hamsters exposed to high concentrations of specially prepared fibrous glass dust obtained from the three largest producers of fibrous glass. One batch was coated with a phenol-formaldehyde resin, another batch was coated with a starch binder, and a third batch was left uncoated. Groups of 30 rats or hamsters were exposed in inhalation chambers for 6 hours/day, 5 days/week for 24 months to concentrations of 106 to 135 mg/m^3 [fiber numbers not provided]. Control groups included 20 rats and 20 hamsters. Samples collected during the experiment indicated that 70% to 76% of the dust was fibrous. The average diameter was 0.5 μm and the average length was about 10 μm (range 5 to 20 μm). Interim sacrifices of 5 animals each were conducted at 6 months and 12 months. The remaining animals were held until their deaths. There were no differences in tissue reactions for the three types of fibrous dusts. The pulmonary response in both species was characterized by relatively small accumulations of macrophages without significant stromal change. No tumors were reported.

Mitchell *et al*. (1986) and Moorman *et al.* (1988) (reporting on the same data) conducted a chronic inhalation study using commercial grade Owens-Corning insulation fiberglass with binder or Tempstran Code 100/475 special-purpose glass fibers without binder. Groups of 50 male and 50 female F344 rats were exposed (whole body) for 7 hours/day, 5 days/week for 86 weeks and held until 80% mortality. The target concentrations were 15 mg/m^3 for the Owens-Corning insulation and 5 mg/m^3 for the 475 glass. There were two exposure groups for each type of glass fiber. One group was exposed to Owens-Corning fibers 4 to 6 μm in diameter and > 20 μm in length, and another group was exposed to shorter and thinner fibers (0.5 to 3.5 μm in diameter and > 10 μm in length). For the 475 glass, the average fiber diameter was < 3.5 μm, but average fiber lengths were > 10 μm in one group and < 10 μm in the other. A control group included 50 male and 50 female rats exposed to filtered and conditioned air.

Pulmonary macrophage aggregates and granulomas that contained glass fibers were observed in treatment groups. Pleural and subpleural plaques resulted from accumulations of granulomatous foci but there was no fibrosis and no evidence of neoplastic lesions in the respiratory tract. Mononuclear-cell leukemia incidence in the

treatment groups ranged from about 35% to 42% compared with 21% in the controls and was statistically significant (Table 4-*2*). The authors speculated that the presence of the glass fibers in the lung and lymphoid tissue might have stimulated cells with a high spontaneous incidence of neoplasia.

Table 4-2. Mononuclear-cell leukemia in rats exposed to glass wool fibers

Group (mg/m^3)	Fiber dimensions (μm)		Incidence (%)		
	diameter	length	Males	Females	Combined
Control	–	–	10/50 (20)	11/49 (22.4)	21/99 (21.2)
Owens-Corning (15)	4–6	> 20	17/50 (34)	20/50 (40)	37/100 (37)*
	0.5–3.5	> 10	18/50 (36)	19/50 (38)	37/100 (37)*
Tempstran 100/475 (5)	< 3.5	> 10	20/50 (40)	15/49 (30.6)	35/99 (35.4)*
	< 3.5	< 10	25/50 (50)	17/49 (34.7)	42/99 (42.4)**

Source: Mitchell *et al.* 1986, Moorman *et al.* 1988.
* $P < 0.05$; ** $P < 0.01$ (compared with controls, Chi square test).

Several inhalation studies of glass fibers in rodents were conducted in the 1980s and reviewed by IARC (1988, 2002). None of these studies showed significantly increased incidences of neoplastic lesions in the respiratory tract. However, all of these studies were considered inconclusive by IARC (2002) because of several technical limitations. In many cases the test fibers were too short, too thick, or were inadequately characterized. Other study limitations included small numbers of animals, inadequate survival data, lung burdens of fibers that were too small or were not reported, whole body instead of nose-only exposure, or the absence of a strong tumorigenic response in positive control groups exposed to asbestos fibers. These studies are not reviewed in detail but are summarized in Table 4-3. Subsequently, a series of inhalation studies in rodents specifically designed to address the limitations of these earlier studies was conducted, and those studies are reviewed in Section 4.1.2. Inhalation studies in primates are reviewed in Section 4.1.3.

Table 4-3. Inhalation carcinogenicity studies of glass wool in rodents published prior to 1988

Test animal	Sex (# animals)	Fiber type (diameter)	Concentration (fiber length)	Exposure protocol[a]	Pulmonary tumor incidence	Comments/limitations	Reference
Rats							
Sprague-Dawley	M (46)	Fiberglass (0.2–6.5 μm)	7.3×10^5 fibers/L, ~168 WHO fibers/cm^3 (> 5 μm)	6 h/d, 5 d/wk, 3 mo (observed at 24 mo)	2/11 (adenoma) 0/13 (controls)	Dust was not fibrogenic, only 7% had an aspect ratio ≥ 3/1, short exposure period, no lung dose, small number of animals at risk due to interim sacrifices, 3/13 tumors in positive controls (amosite)	Lee *et al.* 1981
Wistar	M/F (24/24)	Ground glass wool, resin free (69% < 1 μm)	5 mg/m^3, 48 WHO fibers/cm^3 (42% > 10 μm)	12–24mo (observed at 12, 19, 24 or 28 mo)	1/45 (epidermoid carcinoma)	Type of glass fiber not specified, no lung dose, 9/47 tumors in positive controls (chrysotile)	Le Bouffant *et al.* 1984
	M/F (24/24)	JM100 (95% < 1 μm)	5 mg/m^3, 332 WHO fibers/cm^3 (25% > 20 μm)	5 h/d, 5 d/wk, 24 mo (observed at 28 mo)	0/48	Fibers were relatively short, 9/47 tumors in positive controls (chrysotile)	
F344	M/F (24/24)	JM100 (0.3 μm)	10 mg/m^3 (71% < 10 μm)	7 h/d, 5 d/wk, 12 mo (life)	1/48 (adenoma)	Results from concurrent studies at two laboratories. Fibers were relatively short, 12/48 and 11/56 tumors in positive control groups (chrysotile)	McConnell *et al.* 1984
	M/F (28/27)	JM100 (0.3 μm)	10 mg/m^3 (71% < 10 μm)	7 h/d, 5 d/wk, 12 mo (life)	0/55		
F344	NR (56)	Glass wool, resin and non-resin coated (47%–52% < 1 μm)	10 mg/m^3, 240–320 WHO fibers/cm^3 (58%–72% 5–20 μm)	7 h/d, 5d/wk, 3–12 mo (observed at 3, 12, and 24 mo)	1/48, resin coated (adenocarcinoma) 1/47, non-coated (adenoma)	Type of glass fiber not specified, mass of fibers in lung declined rapidly after exposure stopped, 12/48 tumors in positive controls (chrysotile)	Wagner *et al.* 1984a

Test animal	Sex (# animals)	Fiber type (diameter)	Concentration (fiber length)	Exposure protocol[a]	Pulmonary tumor incidence	Comments/limitations	Reference
	NR (56)	JM100 (97% < 1 μm)	10 mg/m^3, 1,400 WHO fibers/cm^3 (93% < 20 μm)	7 h/d, 5 d/wk, 12 mo (life)	1/48 (adenocarcinoma)	Fibers were relatively short, inadequate survival data, 12/48 tumors in positive controls (chrysotile)	
Osborne-Mendel	F (52)	Insulsafe II with silicon lubricant (1.4 μm)	10 mg/m^3, 100 fibers/cm^3 (37 μm)	6 h/day. 5 d/wk, 24 mo (observed at death)	0/52	Nose-only exposure, non-fiber/fiber ratio 6:1, fibers were short, 3/57 tumors in positive controls (crocidolite)	Smith *et al.* 1987
	F (57–61)	Manville building insulation (1.4 μm)[b]	1.2–12 mg/m^3, 10–100 fibers/cm^3 (31 μm)	6 h/day. 5 d/wk, 24 mo (observed at death)	0/57 (high level) 0/61 (low level)	Nose-only exposure, non-fiber/fiber ratio 38:1, low fiber concentration, 3/57 tumors in positive controls (crocidolite)	
	F (58)	Owens-Corning building insulation (3 μm)[b]	9 mg/m^3, 25 fibers/cm^3 (114 μm)	6 h/day. 5 d/wk, 24 mo (observed at death)	0/58	Nose-only exposure, non-fiber/fiber ratio 31:1, low fiber concentration, fibers were coarse and thick, 3/57 tumors in positive controls (crocidolite)	
	F (57)	Manville Code 100 (0.4 μm)	0.3–3 mg/m^3, 300–3,000 fibers/cm^3 (7.5 μm)	6 h/d, 5 d/wk, 24 mo, nose only (life)	0/57	Low survival in all groups including controls, 3/47 tumors in positive controls (crocidolite)	
Wistar	F (108)	JM104/475 (0.4 μm)	3.0 mg/m^3, 252 WHO fibers/cm^3 (4.8 μm)	5 h/d, 4 d/wk, 12 mo, nose only (life)	1/107 (squamous cell carcinoma)	Fibers were short, 1/100 tumors in positive controls (chrysotile and crocidolite)	Muhle *et al.* 1987
Guinea pigs							
Guinea-pigs	M (32)	Fiberglass (0.2–6.5 μm)	7.3×10^5 fibers/L (> 5	6 h/d, 5 d/wk, 3 mo	2/7 (adenoma) 0/5 (controls)	Fiberglass dust was not fibrogenic but only 7% had an aspect ratio ≥ 3/1,	Lee *et al.* 1981

Test animal	Sex (# animals)	Fiber type (diameter)	Concentration (fiber length)	Exposure protocol[a]	Pulmonary tumor incidence	Comments/limitations	Reference
			μm)	(observed at 24 mo)		short exposure period, no lung dose, small number of animals at risk due to interim sacrifices, no tumors in positive controls (amosite)	
Hamsters							
Hamsters	NR (34)	Fiberglass (0.2–6.5 μm)	7.3×10^5 fibers/L (> 5 μm)	6 h/d, 5 d/wk, 3 mo (observed at 24 mo)	0/9	Fiberglass dust was not fibrogenic but only 7% had an aspect ratio ≥ 3/1, short exposure period, no lung dose, small number of animals at risk due to interim sacrifices, no tumors in positive controls (amosite)	Lee *et al.* 1981)
Syrian golden hamsters	M (60)	Insulsafe II with silicon lubricant (1.4 μm)	10 mg/m^3, 100 fibers/cm^3 (37 μm)	6 h/day. 5 d/wk, 24 mo (observed at death)	0/60	Nose-only exposure, non-fiber/fiber ratio 6:1, fibers were short, no tumors in positive controls (crocidolite)	Smith *et al.* 1987
	M (65–66)	Manville building insulation (1.4 μm)[b]	1.2–12 mg/m^3, 10–100 fibers/cm^3 (31 μm)	6 h/day. 5 d/wk, 24 mo (observed at death)	0/66 (high level) 0/65 (low level)	Nose-only exposure, non-fiber/fiber ratio 38:1, low fiber concentration, no tumors in positive controls (crocidolite)	
	M (61)	Owens-Corning building insulation (3 μm)[b]	9 mg/m^3, 25 fibers/cm^3 (114 μm)	6 h/day. 5 d/wk, 24 mo (observed at death)	0/61	Nose-only exposure, non-fiber/fiber ratio 31:1, low fiber concentration, fibers were coarse and thick, no tumors in positive controls (crocidolite)	
	M (70)	Manville Code 100 (0.4 μm)	0.3–3 mg/m^3, 300–3,000 fibers/cm^3 (7.5 μm)	6 h/d, 5 d/wk, 24 mo, nose only (life)	0/69	Low survival (< 25% to 24 mo) including controls, no tumors in positive controls (crocidolite)	

F = females; M = males; NR = not reported.
[a] Whole-body exposures in inhalation chambers unless otherwise noted.
[b] With phenol-formaldehyde binder.

4.1.2 Later studies in rodents

Beginning in 1988, a series of subchronic and chronic inhalation studies was initiated at the Research and Consulting Company in Geneva, Switzerland to address the limitations of the earlier studies (Bunn *et al.* 1993, Hesterberg *et al.* 1999, Hesterberg *et al.* 1997, Hesterberg *et al.* 1993, Hesterberg *et al.* 1995, McConnell 1994, McConnell *et al.* 1999). The subchronic studies supported an MTD of 30 mg/m^3 (250 to 300 WHO fibers/cm^3) for chronic studies in rats and hamsters (Hesterberg *et al.* 1999, Hesterberg *et al.* 1996a). These studies used nose-only exposure, examined several different types of synthetic fibers in male F344 rats and Syrian golden hamsters, used preparations that contained a large proportion of long fibers (mean length of about 20 μm) and respirable fibers (mean diameters of 1 μm or less), used an exposure protocol (6 hours/day, 5 days/week for 18 months to 2 years) designed to mimic occupational exposure, included at least three exposure concentrations, and included sham-exposed negative controls and asbestos-exposed positive controls (Hesterberg and Hart 2001). Rats were eight weeks old at the beginning of these studies and hamsters were 9 to 15 weeks old. Fibers used in these studies were size separated from commercial glass wools to achieve the desired properties. Approximately 2,000 pounds of bulk insulation product were needed to obtain 20 pounds of size-separated fibers used in the inhalation studies (Hesterberg *et al.* 1993). Hesterberg and Hart (1994) also compared human occupational exposures to glass fibers with exposures used in one of the chronic rat studies and reported that the aerosol used in the rat study was 30-fold more concentrated than the highest human occupational exposures (blowing insulation of unbound fiber glass).

Two other inhalation studies with glass microfibers (100/475 and 104E) and amosite asbestos were conducted at the Institute of Occupational Medicine, Edinburgh, Scotland (Cullen *et al.* 2000, Davis *et al.* 1996). The primary focus of these studies was to compare methods for determining and predicting fiber pathogenicity. The pathogenicity and durability of the different fibers were examined by conducting long-term inhalation and injection studies, *in vitro* tests, and several short-term tests.

Rat

Groups of 112 to 120 male F344 rats were exposed to the respirable fraction of Manville 901 glass wool (MMVF10) or CertainTeed B glass wool (MMVF11) at 3, 16, or 30 mg/m^3 (~30, 150, 240 WHO fibers/cm^3) for 2 years (Bunn *et al.* 1993, Hesterberg *et al.* 1993, Hesterberg *et al.* 1995, McConnell *et al.* 1994). In addition, a recovery group was exposed for 1 year and then held for 1 year without further exposure. The fibers were processed from commercial insulation wools to meet the length and diameter criteria mentioned above. Six animals per group were sacrificed at 3- to 6-month intervals to assess gross and microscopic changes in the lung. Chrysotile and crocidolite asbestos were used as positive controls. The authors stated that fiber-to-fiber comparisons between chrysotile or crocidolite and SVFs are not appropriate because of major differences in fiber dimensions and aerosol concentrations (Hesterberg and Hart 2001). The lungs of exposed groups showed minimal progression of reversible cellular changes and the recovery group showed that alveolar bronchiolization (change from the normal flat to cuboidal epithelium) and granular formation were partially or totally reversed. Bronchoalveolar adenomas occurred in the non-exposed control group and in all but one treatment group. Exposure to insulation glass wools did not cause an increase in lung tumors or mesotheliomas in this study. Incidences of total lung tumors were significantly increased in rats exposed to 10 mg/m^3 chrysotile asbestos (Table 4-4). Many rats in the control and exposed groups showed evidence of mononuclear cell leukemia [incidence data were not provided] involvement of the lung after 24 months (Hesterberg *et al.* 1993). The authors noted that this is a common spontaneous cancer in F344 rats and also occurred in rats which died or were killed in a moribund condition during the study. [Refractory ceramic fibers also were tested in these studies at similar fiber concentrations and dimensions as MMVF10 and MMVF11 (data not shown), and induced significantly increased incidences of lung tumors and mesotheliomas.]

Infante *et al.* (1994) conducted a reanalysis of the Hesterberg *et al.* (1993) data in an attempt to increase the statistical power. Data for the unexposed control group in the glass wool study were pooled with data from unexposed controls in a study with refractory ceramic fibers. Data also were combined across all three dose groups within each glass-wool type or within dose groups for the two insulation glass wools (MMVF10

combined with MMVF11). Results of pairwise comparisons (Fisher's exact test) indicated that rats exposed to MMVF11, but not MMVF10, had significantly increased incidences ($P = 0.027$) of lung tumors (16/350, 4.6%) compared with the pooled controls (7/382, 1.8%). In addition, significant dose-related trends (Cochran-Armitage) were reported for rats exposed to MMVF10 ($P = 0.01$) or MMVF10 and MMVF11 combined ($P = 0.016$). However, Chase and colleagues (Hesterberg and Chase 1996, Rossiter and Chase 1995) have questioned the validity of these statistical reanalyses, arguing that it is inappropriate to ignore inter-study variability and to pool tumor incidences from concurrent and non-concurrent controls and that the lung tumor incidence observed in the concurrent controls was consistent with NTP historical control data.

Davis *et al.* (1996) exposed groups of male Wistar rats to JM100/475 fibers (mean diameter of 0.32 μm) or amosite asbestos. Exposures occurred in inhalation chambers for 7 hours per day, 5 days per week for one year, and the animals were followed for their full life-span. The target concentrations were 1,000 fibers/m^3 > 5 μm in length. Four animals from each group were sacrificed after 12 months and examined for lung pathology and fiber burdens. Fewer long fibers (> 20 μm) remained in the glass fiber-exposed group compared with the amosite group after 12-months exposure. Amosite produced rapid pulmonary inflammation and marked fibrosis and was carcinogenic (7 carcinomas, 9 adenomas, and 2 mesotheliomas). Glass fibers produced less inflammation, very little fibrosis, and benign lung tumors (adenomas) in 4 out of 38 animals (Table 4-4). The four tumors were small (< 1 mm in diameter) and were only found by microscopic examination following layered sectioning of the lung. One pulmonary adenoma and one pulmonary carcinoma occurred in the control group. In a subsequent study from the same group (Cullen *et al.* 2000), an E-glass microfiber (104E) caused increased incidences of lung carcinoma and adenoma combined compared with controls (Table 4-4). Mesotheliomas occurred in 2 of 43 animals but were not observed in controls (*P* value not reported). The authors reported that long fibers from 104E persisted longer than those from JM100/475 and that selective leaching of some components from the 100/475 fibers might have reduced the toxicity. The authors also noted that the latency

period for mesotheliomas was shorter with 104E fibers than with amosite asbestos fibers tested in this study.

Hamster

The inhalation carcinogenicity of MMVF10a, MMVF33, and amosite asbestos was investigated in male Syrian golden hamsters (Hesterberg *et al.* 1997, McConnell *et al.* 1999). (Hesterberg *et al.* presented the preliminary data through 12 months and McConnell *et al.* presented the final data.) Groups of 125 male hamsters were exposed to the respirable fraction of Manville 901 insulation glass wool (MMVF10a) at 30 mg/m^3 (~300 WHO fibers/cm^3 and ~100 fibers longer than 20 μm/cm^3), 6 hours/day, 5 days/week for 78 weeks. MMVF10a was essentially the same as the MMVF10 used in previous studies but had lower fluorine content due to production changes. The average aerosol fiber diameter was 0.95 ± 0.45 μm and the average length was 19.4 ± 20.8 μm. Five animals per group were sacrificed at 13, 26, 52, and 78 weeks to assess gross and microscopic changes in the lung and lung fiber burdens. Recovery groups were removed from exposure after 13 weeks and 52 weeks and held until 78 weeks. Animals remaining after 78 weeks were maintained for a recovery period of about 6 weeks, or until 20% survival. Amosite asbestos (0.8 to 7 mg/m^3) was used as a positive control. The aerosol dimensions and lung doses of the amosite asbestos (0.6 μm diameter) were comparable to those of the test fibers (MMVF10a and MMVF33) (0.9 μm diameter) and may be used for fiber-to-fiber comparisons (Hesterberg and Hart 2001). The initial lung deposition of long fibers (> 20 μm) was similar for glass wool and asbestos, but at the end of the study the lung burden was much less for the MMVF10a group compared with the asbestos groups. After a 6-week recovery period, lung fiber burdens of MMVF10a had declined to near control levels, while amosite fiber burdens had remained the same or increased. Hamsters exposed to MMVF10a showed inflammation which regressed in recovery groups, but no pulmonary or pleural fibrosis or neoplasms. Amosite asbestos induced dose-related inflammation and fibrosis by 13 weeks, which progressed until the end of the study. No lung tumors were observed in the asbestos-treated groups but incidences of mesotheliomas were increased [no statistical comparisons reported]. Data are summarized in Table 4-5.

Table 4-4. Tumor incidences in male rats exposed to glass fibers and asbestos by inhalation

Test animal	Exposure group[a,d]		Lung fiber burden[b] × 10^5	Tumor incidence (%)				Reference(s)
	(mg/m^3)	WHO fibers/cm^3		Lung adenoma	Lung carcinoma	Total lung tumors	Mesothelioma	
F344	Controls	0	0	3/123 (2.4)	1/123 (0.8)	4 (3.3)	0	Hesterberg *et al.* 1993 McConnell 1994 Hesterberg *et al.* 1995
	Chrysotile (10)	10,600	28.1 ± 7.8	7/69 (10.1)	6/69 (8.7)*[c]	13 (18.9)*	1 (1.4)	
	Crocidolite (10)	1,600	NR	10/106 (9.4)	6/106 (5.7)*[c]	15 (14.2)*	1 (0.9)	
	MMVF10 (3)	29	0.24 ± 0.08	0/117 (0)	0/117 (0)	0/117 (0)	0/117 (0)	
	MMVF10 (16)	145	1.85 ± 0.53	1/118 (0.8)	0/118	1/118 (0.8)	0/118 (0)	
	MMVF10 (30)	232	2.88 ± 0.56	6/119 (5.0)	1/119 (0.8)	7/119 (5.9)	0/119 (0)	
	MMVF11 (3)	41	0.48 ± 0.11	3/118 (2.5)	1/118 (0.9)	4/118 (3.4)	0/118 (0)	
	MMVF11 (16)	153	2.35 ± 0.63	6/120 (5.0)	3/120 (2.5)	9/120 (7.5)	0/120 (0)	
	MMVF11 (30)	246	5.03 ± 2.9	3/112 (2.7)	0/112	3/112 (2.7)	0/112 (0)	
Wistar	Controls	0	0	1/38 (2.6)	1/38 (2.6)	2/38 (5.3)	0/38 (0)	Davis *et al.* 1996 Cullen *et al.* 2000
	Amosite (NR)	980	1,230 ± 180	9/42 (21)*[c]	7/42 (17)*[c]	16/42 (38)***	2/42 (4.8)	
	JM100/475 (NR)	1,100	110 ± 110	4/38 (11)	0/38 (0)	4/38 (11)	0/38 (0)	
	104E (NR)	1,000	830 ± 220	3/43 (7)	7/43 (16)*[c]	10/43 (23)*	2/43 (4.7)	

* $P < 0.05$ vs. controls; *** $P < 0.001$ vs. controls (Fisher's exact test).
NR = not reported; WHO fibers/cm^3 = the number of fibers ≥ 5 μm in length, < 3 μm in diameter, with an aspect ratio ≥3:1.
[a]Nose only exposure in studies with F344 rats, whole-body exposures with Wistar rats.
[b] Number of WHO fibers per mg dry lung at 24 months for F344 rats; total lung fiber burden > 20 cm at 12 months in Wistar rats.
[c]Statistics were not reported by the study authors, but results are significant compared with controls by Fisher's exact test.
[d]WHO fibers in the F344 study were similar to total exposure mass of fibers in fibers/cm^3.

No lung tumors were observed in groups of hamsters similarly exposed to MMVF33 (a special-purpose glass fibers prepared by mixing three types of commercially manufactured 475 glass [codes 104, 108B, and 110]) (McConnell *et al.* 1999). Exposure groups included 125 animals each. The unexposed chamber control group included 140 animals. Fiber concentrations were comparable in all groups (~250 to 300 WHO fibers/cm^3) with two lower exposure groups for amosite. Lung clearance was suppressed in the amosite-exposed groups but not in the MMVF 33-exposed group. The number of WHO fibers, and fibers > 20 μm in length, increased in the lung during the 18-month exposure period but were higher in the mid- and high-dose amosite groups than in the MMVF33 group. After 6 weeks of recovery, lung fiber burdens decreased by about 40% in the MMVF33 group compared with a 21% decrease in the high-dose amosite group. Fiber burdens measured in the diaphragm or thoracic wall were lower in the MMVF33 group than in any of the amosite-exposed groups. MMVF33 did produce more severe inflammation than MMVF10a and some mild fibrosis that progressed in severity from week 26 to 52 before leveling off. Incidences of mesothelioma in positive controls were 22 of 85 and 17 of 87 (mid- and high-dose amosite, respectively) compared with 1 of 83 in the MMVF33 group (Table 4-5).

Table 4-5. Tumor incidences in male hamsters exposed to glass wool, special-purpose fibers and asbestos by inhalation

Test animal	Exposure group		Number of animals	Lung fiber burden[a] × 10^6 (WHO)	Mesothelioma (%)
	(mg/m^3)	WHO fibers/cm^3			
Syrian golden hamsters	Controls	0	83	< 0.01 ± 0.01	0
	Amosite (0.8)	36	83	98 ± 20	3/83 (3.6)
	Amosite (3.7)	165	85	356 ± 99	22/85 (25.9)**[b]
	Amosite (7)	263	87	612 ± 147	17/87 (19.5)**[b]
	MMVF10a (30)	339	81	76.7 ± 20.5	0
	MMVF33 (37)	310	83	234 ± 521	1/83 (1.2)

Source: Hesterberg *et al.* 1997, McConnell *et al.* 1999.
** P < 0.01 vs. controls (Fisher's exact test).
[a] Number of fibers per mg dry lung at 78 weeks.
[b] Statistics were not reported by the study authors but results are significant compared with controls by Fisher's exact test.
WHO fibers/cm^3 = the number of fibers ≥ 5 cm in length, < 3 cm in diameter, with an aspect ratio ≥ 3:1.

4.1.3 Studies in primates

Goldstein *et al.* (1983, 1984) compared the effects of inhaled fibrous-glass dust and crocidolite in baboons. Ten male baboons were exposed to 7.5 mg/m^3 (1,100 fibers/cm^3) of glass fibers (a blend of Johns-Manville sample references C102 and C104) or 15.8 mg/m^3 crocidolite. Animals were exposed 7 hours per day, 5 days per week for up to 35 months. Lung biopsies were taken in 2 animals after 8-, 18-, and 30-months exposure and after 6-, 8-, and 12-months postexposure. Surviving animals were kept under observation. The dimensions of the glass fibers were log-normally distributed and were similar to the dimensions of the crocidolite fibers. The diameters ranged from about 0.06 to 8 μm (mean < 1 μm) and lengths ranged from about 0.8 to 58 μm (mean > 5 μm). Fiber content of lung tissue was much higher in crocidolite-exposed baboons (5.6×10^{10} fibers/g) than in glass fiber-exposed baboons (5.0×10^7 fibers/g). Baboons exposed to fibrous-glass dust developed focal peribronchiolar fibrosis with scant ferruginous body formation, but the lesions were much less extensive than observed in the crocidolite-exposed animals. No neoplasms were observed in either group, but the authors noted the relatively short exposure and observation periods.

Mitchell *et al*. (1986) and Moorman *et al.* (1988) reported results from a chronic inhalation study using commercial grade Owens-Corning insulation fiberglass with binder or Tempstran Code 100/475 special-purpose glass fibers without binder (results for studies in F344 rats with the same fibers are reported in Section 4.1.1). Groups of 15 male cynomolgus monkeys were exposed 7 hours/day, 5 days/week for 72 weeks and held until 80% mortality. The target concentrations were 15 mg/m^3 for the Owens-Corning fiberglass and 5 mg/m^3 for the 475 glass. Two exposure groups for each glass fiber type were used. Pulmonary macrophage aggregates and granulomas that contained glass fibers were observed in treatment groups, but no pleural plaques were observed. There was no evidence of fibrosis or neoplastic lesions in the respiratory tract of any treatment group.

4.2 Intraperitoneal administration

In contrast to the inhalation studies, most of the carcinogenicity studies of glass wool fibers administered by i.p. injection (single or multiple doses) resulted in increased incidences of neoplasms (primarily mesothelioma). Two of the studies that reported

results for inhalation exposure to glass fibers (Muhle *et al.* 1987, Smith *et al.* 1987) tested the same fibers by intraperitoneal injections. These studies are reviewed in this section, while many other studies (Adachi *et al.* 2001, Cullen *et al.* 2000, Grimm *et al.* 2002, Lambré *et al.* 1998, Miller *et al.* 1999b, Pott 1987, 1989, Pott *et al.* 1976a, Pott *et al.* 1974, Pott *et al.* 1984a, Roller *et al.* 1996, 1997) were described by their authors as designed to examine the relationship between fiber characteristics and tumorigenicity. Those studies are discussed in Section 4.4.

Most studies included saline-injected controls and asbestos-exposed groups; however, since high-tumor incidences were observed in glass fiber-treatment groups, tumor incidences for asbestos-treatment groups are not shown. The test fibers were administered in 1 to 2.5 mL of saline. In most cases, tumor incidences in asbestos-treatment groups were similar to those reported for glass fiber-treated animals with two notable exceptions. Muhle *et al.* (1987) and Smith *et al.* (1987) reported tumor incidences in asbestos-treatment groups that were about 2.5- to 5-fold higher than in glass fiber-treatment groups. Mesotheliomas were the most common tumor type, but some studies reported sarcomas and carcinomas in a few animals. In many cases, doses exceeded one billion fibers. The strain, sex, number of animals, fiber types, dose and dosing schedule, and results are provided in Table 4-6. Animals were held until their death (generally within 1 to 2.5 years), or sacrificed when moribund.

Smith *et al.* (1987) injected groups of 25 female Osborne-Mendel rats with JM100 and crocidolite asbestos. Test animals received a single injection of 25 mg and were then held until their death. Abdominal mesothelioma occurred in 32% of the animals injected with JM100 and in 80% of the asbestos group. No tumors occurred in the untreated cage controls or saline controls.

Table 4-6. Tumor incidences in rats treated with glass wool fibers by i.p. injection

Strain (Sex)	Treatment group	Dose		No. doses	Tumor incidence (%)[a]	Reference
		mg	% Fibers > 5 μm long			
Wistar (F)	Saline (1 mL)	0	0	1	2/32 (6)[b]	Muhle *et al.* 1987, Pott *et al.* 1987
	JM104[c]	0.5	28%	1	5/30 (17)[b]	
Wistar (M)	JM104	10	NR	1	18/33 (54.6)[b]	
Sprague-Dawley (F)	Saline (2 mL)	0	0	2	3/54 (6)[b]	Pott *et al.* 1987
	JM104	2	NR	1	21/54 (39)[b]	
		2		1	26/54 (48)[b]	
		5		1	44/54 (82)[b]	
		10		1	24/53 (45)[b]	
Osborne-Mendel (F)	Untreated	0	0	0	0/125 (0)	Smith *et al.* 1987
	Saline	0.5 mL	0	1	0/25 (0)	
	JM100	25	56%	1	8/25 (32)	

NR = not reported.
[a] Tumors were mesotheliomas unless otherwise noted.
[b] Includes mesothelioma, spindle-cell sarcoma, and carcinoma combined (very few carcinomas reported).
[c] Results for higher doses of the same fiber type from Pott et al. (1987) are reported in Table 4-9.

4.3 Other exposure routes

Glass fibers also have been tested for carcinogenicity in experimental animals through several other parenteral exposure routes. These include intratracheal instillation, intrathoracic implantation, and intrapleural inoculation. All but one of these studies was conducted in the 1970s and 1980s. Studies were available in rats, hamsters, guinea-pigs, mice, and rabbits. [Results from these studies provide further support for the hypothesis that fiber dimension and durability are important factors in fiber-induced neoplasms.] Studies in rats are summarized in Section 4.3.1. Section 4.3.2 includes studies in hamsters, guinea-pigs, mice, and rabbits. The data from all studies are summarized in Table 4-7.

4.3.1 Rats

In addition to the inhalation study reviewed in Section 4.1.1, Gross *et al.* (1970) exposed groups of 15 to 30 rats and 12 hamsters (discussed in Section 4.3.2) to uncoated, phenol-formaldehyde–coated, or starch binder-coated glass dust by intratracheal injection. Untreated control groups included 20 rats. Fiber dimensions, dosing, and study duration are described in Table 4-7. No differences in pulmonary reaction to coated and uncoated glass dust were noted, and no tumors were observed. Furthermore, no alveolar fibrosis or other significant septal changes in rat lung were reported.

Schepers (1974) summarized about three decades of work investigating the comparative pathogenicity of glass fibers derived from a number of sources. Many of these studies used fiberglass plastic dust where the polymerized resin accounted for 60% to 65% of the total material, while only about 25% of the material was glass fibers. The studies with fiber glass plastic dust are not included in this review. However, several intratracheal injection studies of glass wool or fibrous glass in rats, guinea-pigs, and rabbits were included. These studies used 10 to 21 animals in the exposed groups. No tumors were reported after 12 or 20 months, and the average lung reactions were considered mild in rats.

Pott *et al.* (1987) treated a group of 34 female Wistar rats with 20 intratracheal instillations of 0.5 mg JM104/475 glass fibers. Treatments were given weekly, and the animals were followed for life. A control group of 40 female rats was treated with saline, and another group was treated with crocidolite. Lung tumors (1 adenoma, 2 adenocarcinomas, and 2 squamous-cell carcinomas) occurred in the treatment group but not in the controls. The tumor incidence in the crocidolite group was about 43%, or about three times higher than in the glass-fiber–exposed group. In a similar experiment, 5 weekly intratracheal instillations of 2 mg JM475 glass fibers did not produce tumors in female Osborne-Mendel rats (Smith *et al.* 1987).

Two studies by Stanton *et al.* (1981, 1977) evaluated synthetic glass fibers of different dimensions implanted intrathoracically on the pleural surface, and these studies are discussed in Section 4.4 with other studies that examined a range of fiber characteristics in relation to tumorigenicity. Some, but not all, fibers induced tumors in these studies.

Four intrapleural injection studies in rats were reviewed (Monchaux *et al.* 1981, Wagner *et al.* 1984a, Wagner *et al.* 1976, Wagner *et al.* 1973). No tumors occurred in Wistar rats administered a single injection of 20 mg of JM110 fibers in two experiments; however, 4 of 32 rats injected with 20 mg of JM100 fibers developed mesothelioma (Wagner *et al.* 1976, Wagner *et al.* 1973). Because the JM110 fibers were thicker than the JM100 fibers, the number of injected fibers was about 30 million for JM110 compared with 30 billion for JM100 (Wagner *et al.* 1976). Wagner *et al.* (1984a) treated groups of 48 Sprague-

Dawley rats [sex not specified] by intrapleural injection of resin-coated or uncoated English glass wool and JM100 glass microfiber. Rats received a single injection of 20 mg dispersed in 0.5 mL saline, and a control group of 24 rats was injected with saline. Incidences of mesothelioma were 1 of 48 (glass wool group) and 4 of 48 (JM100 group) (Wagner *et al.* 1984a). Six of 45 Sprague-Dawley rats given a 20-mg dose of JM104 fibers developed mesothelioma (Monchaux *et al.* 1981). Tumor incidences were generally higher in asbestos-exposed groups in each of these studies and ranged from 12.5% to 66%.

4.3.2 Hamsters, guinea-pigs, mice, and rabbits

Vorwald *et al.* (1951) primarily studied the effects of asbestos in long-term inhalation studies using rats, mice, guinea-pigs, rabbits, cats, and dogs, but one intratracheal injection study included a small group of guinea-pigs (6 to 9) exposed to two injections of 25 mg of glass wool. Most of the fibers were 20 to 50 μm in length and were about 3 μm in diameter. Neither lung fibrosis nor tumors were reported after 12 months.

Gross *et al.* (1970) also exposed groups of 12 hamsters to uncoated, phenol-formaldehyde coated, or starch binder-coated glass dust by intratracheal injection. Untreated control groups included 20 hamsters. There were no apparent differences in the pulmonary reaction following exposure to coated or uncoated glass dust, and no tumors were observed. A diffuse, acellular, collagenous pleural fibrosis was noted in some hamsters.

No tumors were reported in guinea-pigs following three intratracheal injections of 75 mg of glass wool, or in rabbits following three intratracheal injections of 300 mg of fibrous glass (Schepers 1974). However, the average lung reactions were considered mild to moderately severe in guinea-pigs and mild in rabbits. No tumors were observed after single intrapleural injections of 10 mg of borosilicate fibers of varying diameters and lengths in groups of 25 mice (Davis 1976, as cited in IARC 2002).

Kuschner and Wright (1976) and Wright and Kuschner (1977) treated groups of 30 guinea-pigs by intratracheal injection of glass fibers of different dimensions. The number of injections varied from 2 to 6, and the total amount injected varied from 12 to 25 mg. Glass fibers were sorted into six groups: short-thin fibers, long-thin fibers, short-very thin

fibers, long-very thin fibers, short-thick fibers, and long-thick fibers. The animals were observed for 24 months. No tumors were reported in any of the groups, but the authors noted that the long glass fibers were fibrogenic.

Two intratracheal instillation studies of JM104 fibers were conducted in hamsters. Pott *et al.* (1984b) reported increased incidences of lung carcinomas, mesotheliomas, and thoracic sarcomas following 8 weekly treatments of 1 mg, while Feron *et al.* (1985) did not report an increase in tumors in hamsters receiving 1 mg every 2 weeks for one year.

Table 4-7. Carcinogenicity studies of glass wool administered by intrapleural or intratracheal inoculation

Test animal (sex)	Fiber type	Fiber dimensions (μm)		Dose (mg × no.)	Route	Study duration	Tumor incidence (%)[a]	Reference
		diameter	length					
Rat- strain								
NR (NR)	Uncoated glass dust	1 (mean)	≤ 50	3.5 × 3 3.5 × 10	i.t.	24 mo	0/15 (0) 0/30 (0)	Gross *et al.* 1970
	Phenol-formaldehyde–coated glass dust	1 (mean)	≤ 50	3.5 × 3 3.5 × 10	i.t.	24 mo	0/30 (0) 0/30 (0)	
	Starch binder-coated glass dust	1 (mean)	≤ 50	3.5 × 3 3.5 × 10	i.t.	24 mo	0/15 (0) 0/30 (0)	
NR (NR)	Controls Fiber glass Glass wool	NA < 2 (20%) < 3-8	NA > 20 (51%) 20-50	0 3.5 × 3 3.5 × 3	i.t.	24 mo 12 mo 20 mo	0/56 (0) 0/10 (0) 0/21 (0)	Schepers 1974
Wistar (F)	Saline JM104/475	0 < 0.18 (50%)	0 > 3.2 (50%)	0.3 mL × 20 0.5 × 20	i.t.	life	0/40 (0) 5/34 (14.7)	Pott *et al.* 1987
Osborne-Mendel (F)	JM100	0.45 (mean)	≤ 20 (94%)	2 × 5	i.t.	life	0/22 (0)	Smith *et al.* 1987
Wistar (M/F)	JM110	1.5–2.5 (30%)	> 20 (60%)	20 × 1	i.pl.	life	0/35 (0)	Wagner *et al.* 1973
Wistar (M/F)	Saline JM110 JM100	0 < 1 (17%) < 0.5 (99%)	0 > 50 (10%) > 20 (2%)	0.4 mL × 1 20 × 1 20 × 1	i.pl	life	0/32 (0) 0/32 (0) 4/32 (12.5)	Wagner *et al.* 1976
Sprague-Dawley (M)	Saline JM104	0 0.23 (mean)	0 5.9 (mean)	2 mL × 1 20 × 1	i.pl	life	0/32 (0) 6/45 (13.3)	Monchaux *et al.* 1981
Sprague-Dawley (NR)	Saline Resin-coated Non-coated	0 < 1 (85%) < 1 (85%)	0 < 5 (70%) < 5 (57%)	0.5 mL × 1 20 × 1 20 × 1	i.pl.	life	0/24 (0) 1/48 (2) [group not specified]	Wagner *et al.* 1984a
Sprague-Dawley (NR)	Saline JM100	0 < 0.6 (95%)	0 < 5 (88%)	0.5 mL × 1 20 × 1	i.pl	life	0/48 (0) 4/48 (8.3)	Wagner *et al.* 1984a

Test animal (sex)	Fiber type	Fiber dimensions (μm)		Dose (mg × no.)	Route	Study duration	Tumor incidence (%)[a]	Reference
		diameter	length					
Hamster- strain								
NR (NR)	Uncoated glass dust	1 (mean)	≤ 50	3.5 × 3	i.t.	24 mo	0/12	Gross *et al.* 1970
	Phenol-formaldehyde coated glass dust	1 (mean)	≤ 50	3.5 × 1 1.75 × 2 3.5 × 3	i.t.	24 mo	0/12 0/12 0/12	
	Starch binder coated glass dust	1 (mean)	≤ 50	3.5 × 3	i.t.	24 mo	0/12	
Syrian golden (M)	Titanium dioxide (granular dust as control)	0	0	1 × 8	i.t.	113 wk	2/135 (1.5)[b] 0/135 (0)[c] 0/135 (0)[d]	Pott *et al.* 1984b
	JM104	< 0.3 (50%)	> 7 (50%)	1 × 8	i.t.	113 wk	6/136 (4.4)[b] 37/136 (27.2)[c] 5/136 (3.7)[d]	
	JM104	< 0.3 (50%)	< 4.2 (50%)	1 × 8	i.t.	113 wk	6/138 (4.3)[b] 26/138 (18.8)[c] 6/138 (4.3)[d]	
Syrian golden (M/F)	JM104	< 1 (88%)	< 5 (58%)	1 × 26 1 × 26	i.t.	85 wk	0/34 (0) 0/30 (0)	Feron *et al.* 1985
Guinea pigs								
Guinea-pigs (NR)	Glass wool	3	20-50	25 × 2	i.t.	12 mo	0	Vorwald *et al.* 1951
Guinea-pigs (NR)	Glass fibers	< 0.6 (95%) < 1 (84%) < 0.3 (100%) < 0.3 (99.7%) > 1 (61%) > 1 (78%)	> 10 (92%) < 10 (93%) < 5 (100%) > 10 (50%) < 10 (87%) > 10 (75%)	4 × 3 12.5 × 2 12.5 × 2 2 × 6 12.5 × 2 12.5 × 2	i.t.	24 mo	0/30 0/30 0/30 0/30 0/30 0/30	Kuschner and Wright 1976, Wright and Kuschner 1977
Guinea-pigs (NR)	Controls Glass wool	0 < 3-8	0 20-50	0 75 × 3	i.t.	24 mo 12 mo	0/150 0/20	Schepers 1974

Test animal (sex)	Fiber type	Fiber dimensions (μm)		Dose (mg × no.)	Route	Study duration	Tumor incidence (%)[a]	Reference
		diameter	length					
	Fiber glass	< 2 (20%)	20-50	75 × 3		12 mo	0/20	
Mouse and rabbit								
BALB/c (NR)	Glass fibers	0.05 (mean) 0.05 (mean) 3.5 (mean) 3.5 (mean)	> 20 < 20 > 20 < 20	10 × 1 10 × 1 10 × 1 10 × 1	i.pl.	≤ 18 mo	0/25 (0) 0/25 (0) 0/25 (0) 0/25 (0)	Davis 1976 (cited in IARC 2002)
Rabbits (NR)	Controls Fiberglass	0 < 2 (20%)	0 > 20 (51%)	0 300 × 3	i.t.	24 mo 8 mo	0/20 0/5	Schepers 1974

i.t.= intratracheal instillation, i.pl. = intrapleural injection, NA = not applicable; NR = not reported.
[a] Primarily mesotheliomas.
[b] Incidence of thoracic sarcomas.
[c] Incidence of mesotheliomas.
[d] Incidence of lung carcinomas.

4.4 Studies of fiber characteristics and tumorigenicity

A number of studies have been carried out to compare various fiber types in order to determine how characteristics of fiber dimensions and durability/biopersistence relate to tumorigenicity. The data from these studies of glass fibers are reported in this section and in Tables 4-8 and 4-9, while the data for all fiber types, which included natural fibers like asbestos and other synthetic mineral fibers like stone wools, that were tested in these studies are reported in Section 5.2. When the chemical compositions of fibers were reported by the authors, the Z-score or Soluble Components Index (KNB) was calculated using the formula reported in Section 1.4. In addition, data on either the biopersistence of fibers, expressed as the half-life *in vivo*, or the dissolution coefficient (K_{diss}) determined *in vitro* and reported in units of ng/cm^2 per hr are reported in Tables 4-8 and 4-9 when available.

The studies by Stanton and Wrench (1972) in the early 1970s compared the tumorigenicity of glass fibers and asbestos applied directly to the lung pleura of rats. Based on incidences of mesotheliomas in the range of 12% to 18% for rats exposed to an especially fine fibrous glass, compared with tumor incidences of 58% to 75% for standard reference samples of amosite, chrysotile, and crocidolite, the authors concluded that long, thin glass fibers were as carcinogenic as similarly sized asbestos.

Stanton *et al.* (1981, 1977) extended these studies with experiments testing the tumorigenicity of 22 glass fiber preparations and other fiber types (see description below and in Section 5.2.1). Based on induction of significant numbers of pleural sarcomas by fine, durable fibers of glass and other fiber types, Stanton *et al.* concluded that fiber dimensions and durability were important in determining the tumorigenicity of the material.

Stanton *et al.* implanted one of either 18 (1977 study) or 22 (1981 study) types of synthetic glass fibers on the pleural surface of the thoracic cavity in groups of 30 to 50 female Osborne-Mendel rats. Other experiments conducted with various natural and synthetic fibers are reviewed in Section 5.2.1. A standard dose of 40 mg of fibers was suspended in gelatin and spread over the surface of flat, 45-mg pledgets composed of autoclaved, binder-coated, coarse fibrous glass (designated as glass #17), which also

served as a control treatment. [This sample was designated glass #18 in Stanton *et al.* (1981).] The pledgets were implanted on the pleural surface via a left-sided open thoracotomy. Most of the glass fibers were flame-attenuated or rotary-processed borosilicate fibrous glasses and were derived from commercial products as received from the manufacturers. The numbers of animals, fiber characteristics, and results are reported in Table 4-8. The samples are identified according to the numbering reported in Stanton *et al.* (1981), which differed slightly from the numbering reported in Stanton *et al.* (1977) because of the addition of a new glass fiber sample identified as Glass #2 in the later paper. The reported tumor incidences were the same in both studies. Tumor incidences were adjusted for survival based on a life-table analysis. Incidences of pleural sarcomas were based on animals surviving the first 52 weeks after treatment and ranged from 0% to 85%.

The statistical comparisons were different in the two studies, in part because the first study examined only glass fibers, while the later study also included a large number of other natural and synthetic mineral fibers. Stanton *et al.* (1977), which examined only glass fibers, divided their experiments into three groups: high-risk, intermediate-risk, and low-risk groups. Incidences of pleural sarcomas in the low-risk group were significantly different from untreated controls, but the authors considered the data to be insufficient to distinguish differences from the treated control group (Glass #18). The low-risk group included experiments 9 to 16 (glasses 10 to 17 in Table 4-8). Tumor incidences in the high-risk group (glasses 1, 3, 4, 5, and 6) and intermediate-risk group (glasses 7, 8, and 9) were significantly higher than in the control group ($P < 0.001$ and $P < 0.01$, respectively). Since the authors drew conclusions based on the dimensions (diameter and length) of the fibers, the fibers are listed in Table 4-8 by dcreasing percentage of fibers with diameter > 1.5 μm or > 2.5 μm.

The results for the 18 glass fiber types tested in the 1977 paper were reported again in Stanton *et al.* (1981) together with one additional glass fiber (designated #2 in that paper) and ~50 additional natural and synthetic fibers (see Section 5.3 and Table 5-1A).

Table 4-8. Carcinogenicity studies of glass wool administered by intrathoracic inoculation with results arranged by percent of fibers below the cutoff values for diameter

Reference (study design)	Fiber Type	$T_{1/2}$, days (95% CI) *in vivo*	Z-score[a]	Diameter, μm	Length, μm	Dose, mg	No. fibers x 10^9	Tumor Incidence (mesothelioma)
Stanton *et al.* 1981, 1977	Glass 1 (SPF)	NR	23.4	< 1.5 (100%)	> 8 (99%)	40	NR	9/17 (85)[c]
	Glass 17 (SPF)	NR	23.4	< 1.5 (93%)	> 8 (24%)	40	NR	0/28 (0)
	Glass 4 (SPF)	NR	23.4	< 1.5 (67%)	> 8 (99%)	40	NR	18/29 (71)[c]
	Glass 6 (SPF)	NR	23.4	< 1.5 (64%)	> 8 (95%)	40	NR	7/22 (64)[c]
	Glass 3 (SPF)	NR	23.4	< 1.5 (49%)	> 8 (97%)	40	NR	20/29 (74)[c]
	Glass 12 (Ins)	NR	42.05	< 1.5 (34%)	> 8 (84%)	40	NR	1/25 (7)[c]
	Glass 5 (SPF)	NR	23.4	< 1.5 (32%)	> 8 (98%)	40	NR	16/25 (69)[c]
	Glass 8 (SPF)	NR	23.4	< 1.5 (25%)	> 8 (76%)	40	NR	3/26 (19)[c]
	Glass 9 (NR)	NR	NR	< 1.5 (19%)	> 8 (95%)	40	NR	2/28 (14)[c]
	Glass 16 (NR)	NR	NR	< 1.5 (16%)	> 8 (62%)	40	NR	1/29 (5)[c]
	Glass 10 (SPF)	NR	23.4	< 1.5 (14%)	> 8 (49%)	40	NR	2/27 (8)[c]
	Glass 7 (SPF)	NR	23.4	< 1.5 (13%)	> 8 (88%)	40	NR	5/28 (21)[c]
	Glass 13 (SPF)	NR	23.4	< 1.5 (4%)	> 8 (60%)	40	NR	1/27 (6)[c]
	Glass 2 (NR)	NR	NR	NR	NR	40	NR	12/31 (77)[c]
	Glass 18[b] (Ins)	NR	23.5	> 2.5 (100%)	> 64 (100%)	40	NR	0/115 (0)
	Glass 11 (SPF)	NR	23.4	> 2.5 (96%)	> 8 (14%)	40	NR	1/27 (8)[c]
	Glass 15 (Ins)	NR	23.5	> 2.5 (98%)	> 8 (96%)	40	NR	1/24 (6)[c]
	Glass 14 (pyrex)	NR	29.4	> 2.5 (98%)	> 8 (90%)	40	NR	1/25 (6)[c]

Source: Stanton *et al.* 1977, 1981.
Ins = insulation glass wool; NR = not reported; SPF = special-purpose fiber.
[a]Z-score calculated from glass composition reported by authors (see Section 1 for formula).
[b]Glass 18 served as the control group and was the vehicle for the implants.
[c]Adjusted for survival by life-table analysis.

Following the studies by Stanton and co-workers, most investigators studying the relationship between fiber characteristics (diameter, length, and durability or biopersistence) have tested fibers by intraperitoneal injection. The authors of these studies generally agreed with the concept put forward by Stanton and co-workers that carcinogenicity is related to fiber dimensions and biopersistence, but the authors' conclusions are discussed further below and in Section 5.2.2. The results of the studies with glass fibers are reported in Table 4-9.

Pott *et al.* (1974) investigated the tumorigenic effects of various fibrous dusts, including sodium-calcium borosilicate glass fibers, in Wistar rats. About 73% of the fibers were < 5 μm in length and the average diameter was about 0.5 μm. A group of 40 rats (sex not specified) was given four weekly injections of 25 mg of glass fibers. The control group received four injections of saline. No tumors occurred in the control group, but more than half of the treatment group (23/40) developed mesotheliomas. Based on their results they suggested that fibers less than 10 μm in length could still be carcinogenic, and similarly, they proposed that carcinogenicity could not be limited to fibers with diameter less than 0.5 μm.

Pott *et al.* (1976a) investigated the carcinogenicity of a number of fibrous dusts in groups of female Wistar rats. [The paper was published in German with an English abstract.] Rats were administered single injections of 2 or 10 mg of S&S106 glass fibers (59% fibers < 3 μm long) or MN104 [identified as JM104 by IARC 2002] (mean fiber dimensions 10 μm × 0.2 μm). [The S&S 106 glass fibers were identified as German glass wool by IARC 2002 and reported in a section of insulation glass wools; however, the source of these fibers was the German company, Schleicher and Schuell, of Dassell, Germany, which is now part of the Whatman Group and manufactures glass fibers for filtration (i.e., special-purpose fibers). No other information on the characteristics of these fibers was identified.] Other groups were treated with four weekly injections of 25 mg of glass wool, two weekly injections of 25 mg of MN104, or a single injection of 20 mg of MN112 [identified as JM112 by IARC 2002] (mean fiber dimensions 30 μm × 1 μm). In addition, several groups were treated with various doses of chrysotile asbestos. Hamsters were administered single injections of 2 or 10 mg of glasswool. The animals

were held until natural death. Dose-dependent increases in incidences of mesotheliomas were reported, ranging from 3% to 72% in glasswool treatment groups, 27% to 71% in MN104 treatment groups, and 38% in the MN112 group. Other tumor types also were reported. Spindle-cell sarcoma was the most common tumor type, occurring in most treatment groups at 4% to 8%. Tumor incidences in asbestos-treated groups ranged from about 16% to 81%. No tumors were reported in 72 saline-treated rats. [The English abstract reported that i.p. injection of fibrous dusts also induced mesotheliomas in mice, but not in Syrian golden hamsters or guinea-pigs. However, no data were presented for these animals.]

Pott *et al.* (1984a) tested some of the same fibers as in their previous publications, but they also injected JM100 and JM104 glass fibers into female Wistar or Sprague-Dawley rats. The percentage of either Wistar or Sprague-Dawley rats that developed abdominal tumors after i.p. injection of JM104 glass fibers decreased after pretreatment of the fibers for 2 or 24 hours with 1.4 N NaOH, which resulted in loss of 1.7% to 6.8% of the starting weight of the fibers. Pretreatment with 1.4 N HCl for 24 hours, which resulted in the loss of approximately one third of the starting weight of the fibers, almost totally eliminated tumor development in either strain of rats followed for more than 450 days after injection (see Figure 4-1). The fiber dimensions were affected only slightly by the pretreatments, and the authors reported that the loss of fiber weight was not associated with any discernible corrosion of the fibers examined by scanning electron microscopy. (The authors noted that two different batches of JM104 fibers differed in the amount of weight lost after treatment with hydrochloric acid, which led them to conclude that the two samples must have had different chemical compositions.) Pott *et al.* did propose that the considerable reduction in carcinogenicity with HCL pretreatment might have been due to alterations in the rate of dissolution or disintegration of the fibers or their migration within tissues, but they did not consider these hypotheses as proven by their data.

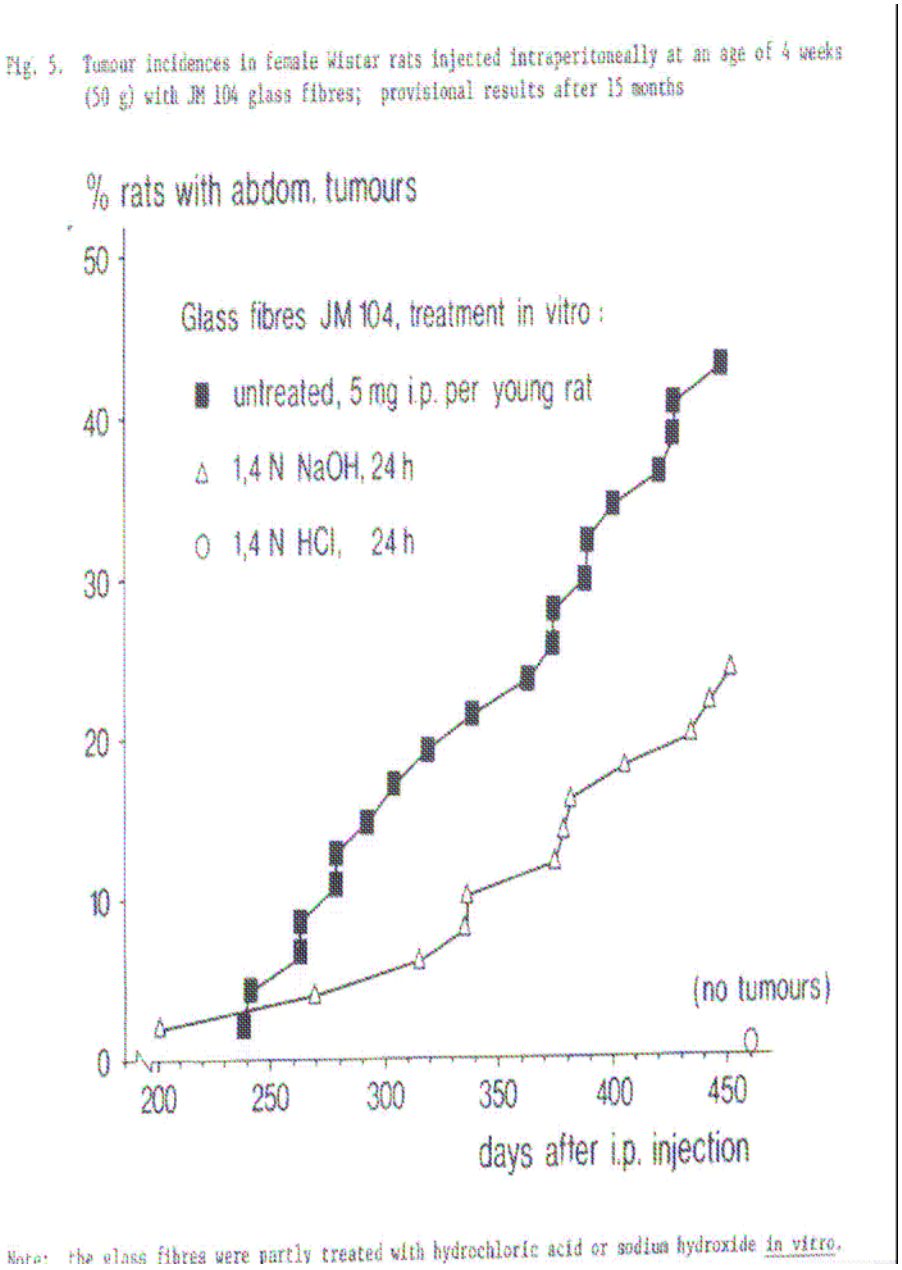

Figure 4-1. Effects of fiber pretreatment with sodium hydroxide (NaOH) or hydrochloric acid (HCl) on tumorigenicity
Source: Pott *et al.* 1984a

A series of other experiments by Pott and co-workers (Muhle *et al.* 1987, Pott 1989, Pott *et al.* 1984a, Pott *et al.* 1987) was conducted specifically to investigate the relationship of fiber dimensions and durability with carcinogenic potency. These studies examined the carcinogenicity of JM100 and JM104 microfibers as well as several other types of mineral fibers, including asbestos. In the first study, groups of 37 to 45 female Wistar rats

were given single i.p. injections of 2 mg of JM100 or JM104 microfibers (Pott *et al.* 1984a). Other groups received 10 mg of JM104. Two batches of JM100 fibers were used that had slightly different size distributions. Several batches of JM104 fibers were used that were subjected to 1 to 4 hours of milling in a ball mill before use. The authors reported incidences of mesothelioma and sarcoma combined. JM100 fibers induced a low incidence of tumors (5%). The authors noted that these fibers were relatively short (90% were < 7.3 μm in one batch and < 3.1 μm in the other batch). Tumor incidences were higher in the JM104-treatment groups, presumably due to longer fibers. The lowest tumor incidence in rats treated with JM104 (9%) occurred with shorter and thicker fibers relative to the other JM104 groups. The authors also noted in a footnote to one table that the tumor incidence could have been reduced in this group due to an infection at 21 months, but no other details were provided. Subsequent studies with JM104 fibers in male and female Wistar rats and female Sprague-Dawley rats resulted in tumor incidences of about 17% to more than 80%. Tumor incidences in the saline controls ranged from about 2% to 6%. All abdominal tumors (including mesothelioma, sarcoma, and carcinoma) were combined; however, very few carcinomas occurred. The authors noted that the three tumor types could not always be differentiated.

Pott *et al.* (1991) conducted a comparative carcinogenicity study of some experimental fibers having a relatively low biodurability (B-1 and B-2) and fibers having greater biodurability (B-3 and JM104). The mean half-lives were 38 days for B-2 glass wool, 107 days for B-1 glass wool, and 238 days for B-3 glass wool. [No half-life was reported for JM104 fibers.] Female Wistar rats received one to three injections of experimental fibers (B-1, B-2, and B-3) at the doses and number of fibers shown in Table 4-9, or a single injection of 2 mg of JM104. The median diameters of the fibers were 0.14 μm (JM104), 0.35 μm (B-3), 0.5 μm (B-2), and 1.5 μm (B-1). Both the dose and length of the fibers were varied, with fibers designated as either K (kurz, German for short), M (medium), or L (lange, German for long). The Z-scores calculated for the fibers were lowest for B-3 fibers (15.7) and highest for B-1 and B-2 fibers (35.8), which had the same chemical composition (see Section 1, Table 1-4). The authors concluded that a carcinogenic effect could be detected only in groups injected with durable glass fibers (B-3 or JM104), and

that slightly durable glass fibers (B-1 and B-2) did not induce a carcinogenic effect at the doses and fiber sizes tested, which included up to 5.80×10^9 B-2 fibers with median length of 6 μm and median diameter of 0.51 μm.

Roller *et al.* (1996) conducted a study designed to examine the dose-response relationship for fiber types of different dimensions and *in vivo* durabilities. Incidences of mesotheliomas ranged from 3% to 70% for glass fibers, while incidences of mesothelioma in asbestos-treated groups ranged from 23% to 80%. These studies investigated several types of SVFs, including samples from at least four commercial insulation wools, and an experimental glass fiber type (B-01) of low biodurability (mean $T_{1/2}$ = 32 days). Each of these studies followed the same general design. Groups of at least 32 Wistar rats (usually female) were given single or multiple i.p. injections of ~10^7 to > 10^{10} fibers (length > 5 μm) and were observed for 30 months. Results are reported in Table 4-9, and discussed below.

The relationship between fiber dimensions and tumorigenicity were discussed in Roller *et al.* (1997). The fibers were divided into groups of relatively long, thick fibers (aspect ratio > 5:1, median length 8–17 μm, median diameter 0.7–1.2 μm) and short, thin fibers (aspect ratio > 5:1, median length 2–4 μm, median diameter 0.2–0.5 μm). The long, thick fibers included the following glass fiber types: B-09-0.9, B-09-2.0, B-20-2.0, and MMVF11. The short, thin fibers included the following glass fiber types: B-09-0.6, B-20-0.6 [reported as B-0.9-0.6 in Table #1 in Roller *et al.* (1997), but the doses matched the results reported for fiber type B-20-0.6 in Table #4 in Roller *et al.* (1996)] and M-753-105. The overall conclusion by Roller *et al.* (1997) was that the mechanism responsible for mesotheliomas in their experimental system was specific to the fibrous shape of the particles administered based on parallelism of the probit lines calculated for each fiber type (see Section 5.2.2 and Figure 5-3).

Lambré *et al*. (1998) evaluated the carcinogenic potential of two glass wools (Fiber A and Fiber C) described as sodium-modified borosilicates (see Table 4-9). The samples had been specially manufactured and processed to produce fibers in the size range with median diameter less than 1 μm and median length between 10 and 15 μm. Fiber

durability (K_{diss}) was 129 ng/cm^2 per hour for Fiber A and 309 for Fiber C. Both fiber types had a Z-score of 26.7. These fibers were administered to groups of 51 female Wistar rats by i.p. injection (one or two injections) at 0.7, 2.1, 7, or 17.5 mg/dose. Crocidolite (0.005, 0.05, or 0.5 mg) was used as a positive control. The study was stopped at week 130 when the survival rate had reached 20% in the control groups. Survival was the same in groups injected with glass fibers as in the negative control groups. Adhesions involving various abdominal organs were noted in the treatment groups. Fibrosis increased with dose, and a few mesotheliomas occurred in the groups treated with Fiber A or Fiber C. Incidences of mesothelioma in asbestos-treated groups ranged from 7.8% to 39.2%. The authors concluded that the glass fibers tested in this study did not show a carcinogenic potential at the tested doses, and their general conclusion was that fibers with a high dissolution rate *in vitro* at pH 7.4 along with low biopersistence for fibers with length > 20 mm tended to have a low carcinogenic potency in the i.p. assay. Tumors were induced by several stone wools tested in the same study (see Section 5.2.2).

Miller *et al*. (1999b) and Cullen *et al.* (2000) investigated the carcinogenic effects of a number of SVFs, including MMVF10 glass wool and two special-purpose glass microfibers (JM100 and 104E) (see Table 4-9). Durability (K_{diss}) was 122.4 ng/cm^2 per hr for MMVF10 and 9.1 for JM100. The i.p. dose was selected as a mass sufficient to contain 10^9 fibers > 5 μm in length. Treatment groups consisted of 18 to 24 male Wistar rats. Positive controls were treated with 6.1 mg of amosite asbestos. These studies did not include negative controls. Animals were maintained until they showed signs of debilitation. Miller *et al.* (1999b) reported that carcinogenicity was linked to the number of injected fibers > 20 μm in length and the biopersistence of fibers > 5 μm in length. The incidence of mesotheliomas was 59% in the glass wool group, 33% in the JM100 group, 88% in the 104E group, and 88% in the asbestos group. Although tumor incidences were similar for the 104E and asbestos groups, tumors appeared earlier in the 104E group. In particular, Cullen *et al.* (2000) speculated that differences in surface properties (i.e., selective leaching of some glass components) might also be important for explaining the greater effect of 104E glass compared with 100/475 fibers.

Adachi *et al*. (2001) administered glass wool or micro glass fibers to groups of female F344 rats by i.p. injection (10 to 20 mg) and observed the animals for 2 years. Chrysotile asbestos and several SVFs were included in this study. No tumors were reported for the groups exposed to glass wool or micro glass fiber, but very few details were provided.

In the most recent study, Grimm *et al.* (2002) investigated the carcinogenic potential of three newly developed biosoluble insulation glass wool fibers (designated M, P, and V) and compared these with previously developed soluble B glass fiber (reported by the authors as considered non-carcinogenic in the German TRGS 905) (see Table 4-9). The dissolution coefficients (K_{diss}) for the fibers were 580 ng/cm^2 per hour for B, 103.7 for M, 610 for P, and 450 for V. Z-scores could be calculated for P (45.45) and V (26.36) fibers only. Prior to administration, the fibers were processed to reduce the amount of non-WHO fibers and nonfibrous particles. Groups of 50 to 53 female Wistar rats were given 2, 8, or 20 i.p. injections of the various glass fibers. Crocidolite (0.5 or 5 mg) was used as a positive control. The study was terminated after 123 weeks. Fiber M did not show a carcinogenic response, while Fibers P and V showed a slight carcinogenic response similar to that for B fibers. Although fibers B (17%), P (15%), and V (27%) significantly increased tumor levels [statistical test and level of significance not reported], the authors reported that all of the fibers met the EC criteria for exoneration from carcinogenicity classification. Incidences of mesotheliomas in the asbestos groups were about 53% to 88%. Also, they noted that no statistical difference was found between fiber B and any of the other fibers, and that fiber B was named in the German TRGS 905 as a fiber that is not considered to have carcinogenic potential. The authors speculated that the German criterion based on a dose of 5×10^9 WHO fibers might not be valid for highly soluble mineral fibers.

Table 4-9. Tumor incidences in rats treated with glass wool fibers by i.p. injection

Strain (Sex)	Treatment group	Biopersistence, $T_{1/2}$, days (95% CI) *in vivo*	Z-score	Diam. (median) μm	Length (median) μm	Dose		No. doses	Tumor incidence (%)[a]	Reference
						mg	Fibers × 10^9 or % > 5 μm long			
Wistar (NR)	Saline (2 mL)	–	–	–	–	0	0	4	0/80 (0)	Pott *et al.* 1974
	Glass fiber	NA	NA	0.5 (avg.)	72.6% < 5	25	~27%	4	23/40 (57.5)	
Wistar (F)	Saline (2 mL)	–	–	–	–	0	0	4	0/72 (0)	Pott *et al.* 1976a
	German glass wool (S&S 106)	NA	NA	NA	NA	2	0.024	1	1/34 (3)	
						10	0.12	1	4/36 (11)[b]	
						25	1.2	4	23/32 (72)[b]	
	MN104 [JM104]	NA	NA	NA	NA	2	NR	1	20/73 (28)[b]	
						10		1	41/77 (53)[b]	
						25		2	55/77 (71)[b]	
	MN112 [JM112]	NA	NA	NA	NA	20	NR	1	14/37 (38)[b]	
Wistar (F)	JM100	NA	NA	0.33	2.4	2	NR	1	2/44 (5)[b]	Pott *et al.* 1984a
				0.24	1.4	2		1	2/44 (5)[b]	
	JM104	NA	NA	0.29	4.8	2	NR	1	14/44 (32)[b]	
				0.29	4.8	10		1	27/37 (73)[b]	
				0.29	4.8	10		1	29/44 (66)[b]	
				0.29	4.8	10		1	19/39 (49)[b]	
				0.39	2.7	10		1	4/45 (9)[b]	
Wistar (F)	Saline (1 mL)	NA	NA	–	–	0	0	1	2/32 (6)[b]	Muhle *et al.* 1987, Pott *et al.* 1987
	JM104	NA	NA	0.18	3.2	0.5	28%	1	5/30 (17)[b]	
						2	NR	1	8/31 (26)[b]	
						5	NR	1	20/45 (44)[b]	
						10	NR	1	13/26 (50)[b]	
Wistar (M)	JM104	NA	NA	NA	NA	10	NR	1	18/33 (54.6)[b]	

Strain (Sex)	Treatment group	Biopersistence, $T_{1/2}$, days (95% CI) *in vivo*	Z-score	Diam. (median) μm	Length (median) μm	Dose		No. doses	Tumor incidence (%)[a]	Reference
						mg	Fibers × 10^9 or % > 5 μm long			
Sprague-Dawley (F)	Saline (2 mL)	–	–	–	–	0	0	2	3/54 (6)[b]	Pott *et al.* 1987
	JM104	NA	NA	NA	NA	2	NR	1	21/54 (39)[b]	
						2		1	26/54 (48)[b]	
						5		1	44/54 (82)[b]	
						10		1	24/53 (45)[b]	
Wistar (F)	Saline (2 mL)	–	–	–	–	0	0	5	2/102 (2)[b]	Pott *et al.* 1989
	JM104	NA	NA	0.15	2.6	1	0.68	5	34/53 (64)[b]	
Wistar (F)	Saline (2 mL)	–	–	–	–	0	0	5	2/50 (4)[b]	Pott *et al.* 1991[c]
	B-1K	107	35.8	1.06	7.4	20	0.24	3	3/46 (7)[b]	
	B-1K	(98–119)		1.06	7.4	50	0.60	3	1/32 (3)[b]	
	B-1M			1.68	10.7	20	0.05	1	1/48 (2)[b]	
	B-1M			1.68	10.7	20	0.16	3	1/46 (2)[b]	
	B-1ML			1.19	11.0	50	0.51	2	1/39 (2)[b]	
	B-1L			1.40	17.8	20	0.04	1	1/48 (2)[b]	
	B-1L			1.40	17.8	20	0.11	3	5/46 (11)[b]	
	B-2K	38	35.8	0.49	4.2	6.7	0.29	1	0/48 (0)	
	B-2K	(35–41)		0.49	4.2	20	0.86	1	0/46 (0)	
	B-2L			0.51	6.0	6.7	0.39	1	0/45 (0)	
	B-2L			0.51	6.0	20	1.16	1	2/44 (5)[b]	
	B-2L			0.51	6.0	50	5.8	2	1/35 (3)[b]	
	B-3K	238	15.7	0.37	3.3	6.7	0.38	1	10/48 (21)[b]	
	B-3K	(183–340)		0.37	3.3	20	1.14	1	30/47 (64)[b]	
	B-3L			0.34	5.6	6.7	0.15	1	19/48 (40)[b]	
	B-3L			0.34	5.6	20	0.46	1	31/47 (66)[b]	
	JM104	NR	21.0	0.40	10.60	2	0.32	1	8/48 (17)[b]	

Strain (Sex)	Treatment group	Biopersistence, $T_{1/2}$, days (95% CI) *in vivo*	Z-score	Diam. (median) μm	Length (median) μm	Dose		No. doses	Tumor incidence (%)[a]	Reference
						mg	Fibers × 10^9 or % > 5 μm long			
Wistar (F)	Saline (2 mL) MMVF11	– 199 (172–235)	– 27.1	– 0.77	– 14.6	0 35 30	0 0.4 1.0	3 2 6	0/38 (0) 12/40 (30) 16/23 (70)	Roller *et al.* 1996, 1997
	Saline (2 mL) M 753	– NA	– 24.8	– 0.22	– ~3.3	0 17 50	0 1 2.9	3 1 1	0/38 (0) 30/40 (75) 36/40 (90)	
Wistar (F)	Untreated Saline (2 mL) B-01-0.9	– – 32 (26–45)	– – 35.8	– – ~0.7	– – 9.60	0 0 25 25 25	0 0 2.5 5.0 10	0 20 5 10 20	0/37 (0) 0/93 (0) 3/39 (8) 4/37 (11) 3/36 (8)	
Wistar (M)	Saline (2 mL) B-01-0.9	– 32 (26–45)	– 35.8	– ~0.7	– 9.60	0 25 25	0 10 20	0 20 40	1/69 (1) 10/48 (21) 33/50 (66)	
Wistar (F)	Saline (2 mL) B-09-0.6	– NA	– 26.7	–	–	0 50 50	0 2.0 6.1	3 2 6	0/38 (0) 1/40 (3) 4/39 (10)	
	Saline (2 mL) B-09-2.0	– NA	– 26.7	– 0.49	– 3.3	0 50 50	0 1.1 3.2	3 3 9	0/38 (0) 9/40 (23) 21/40 (53)	

Strain (Sex)	Treatment group	Biopersistence, $T_{1/2}$, days (95% CI) *in vivo*	Z-score	Diam. (median) μm	Length (median) μm	Dose		No. doses	Tumor incidence (%)[a]	Reference
						mg	Fibers × 10^9 or % > 5 μm long			
Wistar (F)	Saline	–	–	–	–	0	0	0	0/102 (0)	Lambré *et al.* 1998
	Fiber A	129 (K_{diss})[d]	26.7	0.70	24.6	0.7	0.009	1	2/51 (4)	
						2.1	0.027	1	0/51 (0)	
						7.0	0.092	1	0/51 (0)	
						17.5	0.460	2	1/51 (2)	
	Saline	–	–	–	–	0	0	0	0/102 (0)	
	Fiber C	309 (K_{diss})	26.74	0.69	27.2	0.7	0.013	1	1/51 (2)	
						2.1	0.038	1	1/51 (2)	
						7.0	0.126	1	0/51 (0)	
						17.5	0.630	2	0/51 (0)	
Wistar (M)	MMVF10	122.4 (K_{diss})	NA	NA	> 5	144	0.66	1	13/22 (59)	Miller *et al.* 1999b
	JM100	9.1 (K_{diss})	16	NA	> 5	8.3	1.87	1	8/24 (33)	
Wistar (M)	104E	NA	NA	NA	NA	12.6	~1	1	21/24 (88)	Cullen *et al.* 2000
F344	Glass wool	NA	NA	NA	NA	10	NR	1	NR (0)	Adachi *et al.* 2001
	Micro fiber glass	NA	NA	NA	NA	10			NR (0)	

Strain (Sex)	Treatment group	Biopersistence, $T_{1/2}$, days (95% CI) *in vivo*	Z-score	Diam. (median) μm	Length (median) μm	Dose		No. doses	Tumor incidence (%)[a]	Reference
						mg	Fibers × 10^9 or % > 5 μm long			
Wistar (F)	Untreated	–	–	–	–	0	0	0	0/51 (0)	Grimm *et al.* 2002
	Saline (2.5 mL)	–	–	–	–	0	0	20	0/51 (0)	
	B glass	580 (K_{diss})	34.42	0.52	8.90	216	2	8	3/51 (2)	
						541	5	20	9/53 (17)	
	M glass	103.7 (K_{diss})	30.04	0.41	7.70	41	0.5	2	0/50 (0)	
						164	2	8	0/51 (0)	
						410	5	20	0/52 (0)	
	P glass	610 (K_{diss})	45.45	0.40	9.60	51	0.5	2	0/51 (0)	
						205	2	8	4/51 (8)	
						512	5	20	8/52 (15)	
	V glass	450 (K_{diss})	26.36	0.80	9.90	72	0.5	2	2/51 (4)	
						290	2	8	1/51 (2)	
						724	5	20	14/51 (27)	

NR = not reported.
[a] Tumors were mesotheliomas unless otherwise noted.
[b] Includes mesothelioma, spindle-cell sarcoma, and carcinoma combined (very few carcinomas reported).
[c] B-1 and B-2 are experimental low-durability glass wool; B-3 is an experimental durable glass fiber. K, M, and L designate short, medium, and long fiber ranges, respectively.
[d] K_{diss} = dissolution coefficient *in vitro*, reported in units of ng/cm^2 per hr.

4.5 Routes of exposure

Three primary test models have been used to evaluate the toxicity and carcinogenicity of fibers in rodents: inhalation exposure, intratracheal instillation of fiber suspensions, and direct exposure of the pleura or peritoneum by injection of fiber suspensions into the thoracic or abdominal cavity (see Section 4). IARC (2002) acknowledged that "there is no general agreement on which of these routes of administration best predicts human cancer risk." However, the available data demonstrate that chronic i.p. injection studies and inhalation toxicity studies provide the same relative ranking of fiber pathogenic potential (Bernstein 2007a, Bernstein et al. 2001a, 2001b). This section discusses interspecies comparisons between rats and humans, and the different types of animal models used to test for carcinogenicity.

4.5.1 Interspecies comparison

There is debate on whether humans are more sensitive to fiber carcinogenicity (from inhalation exposure) than rats (Maxim and McConnell 2001, Muhle and Pott 2000, Roller and Pott 1998). This debate stems from evaluation of the the body of literature on asbestos. Various investigators have compared the sensitivity of humans and rats to asbestos-induced carcinogenicity and have arrived at different conclusions. Muhle and Pott (2000) and Roller and Pott (1998) compared cancer risks for humans using the epidemiologic data (primarily from Health Effect Institute-Asbestos Research and Doll and Peto (1985); data from U.S. EPA and U.S. OSHA provide similar risk estimate) and animals using data on asbestos inhalation studies. They concluded that rats required more than 100 times higher fiber concentrations to match the lung cancer risk (Figure 4-2) of asbestos workers and 1,000 times higher to match the mesothelioma risk. In a later publication (Wardenbach *et al*. 2005), they created a scatterplot of the tumor response in rat inhalation studies from several studies and human and epidemiological data from multiple studies (in response to criticism for using a single point, see below) for amphibole and chrysotile asbestos. According to the authors, this analysis still showed a greater sensitivity for humans compared with rats for both amphibole asbestos and chrysotile asbestos (when compared with textile studies, which were considered by the authors to have the purest asbestos exposure). They did not think that the shorter exposure duration in the animal studies should be taken in account when comparing

sensitivities since comparisons should be based on lifespan rather than absolute time units. These authors concluded that the rat inhalation model is not sufficiently sensitive to show a carcinogenic response for fibers.

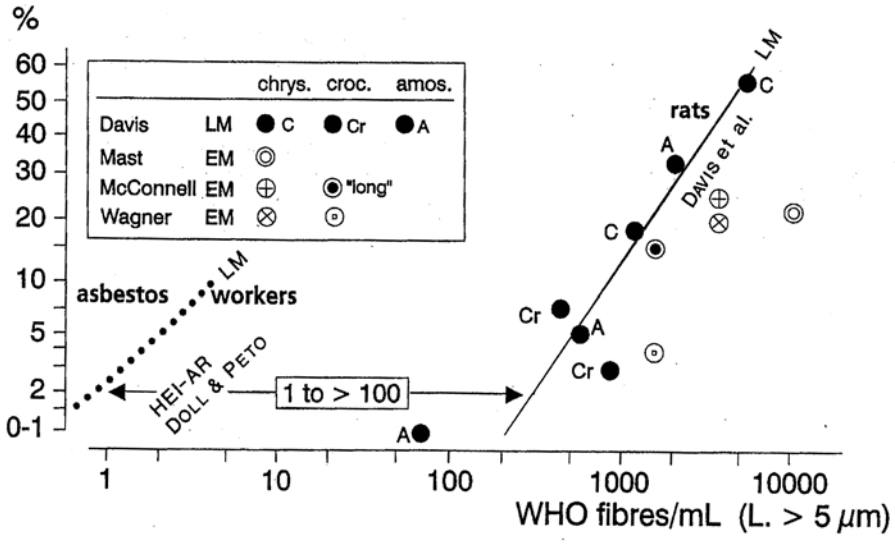

Figure 4-2. Tumor incidence for epidemiologic studies (humans) and chronic inhalation studies (rats) for exposure to asbestos.

The dotted curve on the left-hand side: increasing tumor risk from asbestos fibers for workers (excluding mining and milling) after 25 years occupational exposure when the fiber concentration increases from 1 to 5 fibers per mL (Doll and Peto 1985, HEI-AR 1991). Measurement points on the right-hand side: association between much higher fiber concentrations in the air of chronic inhalation studies with rats and tumor response. Exposure in the majority of the experiments: 35 hours/week for one year. Data of Davis *et al.* (1986a, 1978), Davis and Jones (1988), Mast *et al.* (1995a, 1995b), McConnell *et al.* (1994, 1984), Wagner *et al.* (1984b, 1985). The fiber concentration in the workplace atmosphere and in the inhalation chambers of Davis and co-workers are related to light microscopial (LM) measurements; electron microscopy (EM) has been used in the other inhalation experiments. The regression line has been calculated from the results of Davis *et al.* (black dots). (From Muhle and Pott 2000)

In contrast to this, Maxim and McConnell (2001) conducted an interspecies comparison of the toxicity of asbestos and SVF and concluded that there is *no reason to conclude that humans are more sensitive to fibers than rats with respect to the development of lung cancer*. They stated that a comparison of tumor data from several animal studies with only one estimate of potency in humans could be misleading, given that potency estimates in human epidemiologic studies vary substantially, and that some of the apparent differences in sensitivity might be explained by the synergistic effects of asbestos exposure and smoking. They also thought exposure duration should be considered when conducting interspecies analyses. They cited an analysis conducted by

Rowe and Springer (1986) that used data from 5 epidemiologic studies and animal data from one publication (Wagner *et al.* 1974) in an analysis that included exposure duration (working lifetime of 45 years with 8 hours per day and 250 days per year). This analysis found that risks estimated by the animal study were within the range of the risk estimates from the human studies. [Wardenbach *et al.* criticized the use of only the Wagner data in this analysis since the study only provided mass concentrations (not fiber), and in general the high tumor incidences in this study have not been replicated in other studies in experimental animals.]

Maxim and McConnell (2001) also discussed factors related to dosimetry (exposure and lung burden) and fiber toxicity and concluded that the rat is preferable as a model for lung cancer. In addition to the points discussed above, they made the following conclusions:

1. Deposition and clearance: Modelling studies that normalize for lung weight show that the relative deposition of SVFs (number of fibers per unit time) in humans is smaller than that for rats, and that fiber clearance (based on models and data using refractory ceramic fiber) is faster in rats than humans. The authors also pointed out that clearance can be reduced by high particle overload, which has been demonstrated in rats.

2. The sensitivities of human and rodent cells appear to have comparable sensitivity with regard to fiber-induced cytotoxicity, production of inflammatory components (i.e., cytokines), transformation, and proliferation.

3. The available data suggest that lung fiber burdens associated with fibrosis are similar in rats and humans, although exact comparisons are limited by the paucity of information on the fibers' (asbestos) length, diameter, and distribution in the lung.

4. Humans and rats are equally sensitive to development of fiber-induced lung cancer based on studies with asbestos and refractory ceramic fibers (see above).

5. Lifespan of animals: The authors stated that the rate of dissolution of fibers is similar in rats and humans, and since humans live longer, the rat model might not take into account the effects of clearance.

4.5.2 Animal models

Inhalation studies

In principle, the most relevant route of administration used in animal studies is the route that mimics human exposure. Inhalation is the primary route of exposure to fibers; however, inhalation experiments with fibers present some unique challenges. These include sample preparation, size selection, and aerosol generation methods; determination of the MTD; whole-body or nose-only exposure; differences in the respiratory tract and respiration in rodents and humans; differences in respirable fiber dimensions, deposition, clearance, and retention in rodents and humans; selecting the best animal model; and sensitivity and potency issues. All of these are relevant factors for interpreting results from the available inhalation studies (Oberdörster 1996).

The primary advantages of fiber inhalation studies include use of a natural route of exposure: lung defenses are not bypassed, and lung biopersistence and toxicity and mechanisms for lung tumor induction can be examined. The disadvantages are that inhalation studies are complex, time-consuming, costly, and may lack sufficient sensitivity for detecting fiber-induced cancers under experimental conditions. Furthermore, there is no general consensus on which animal species is (are) best for predicting effects in humans (Oberdörster 1996). Although the rat model is the most common, there is some evidence that the hamster might be more appropriate for detecting mesotheliomas (Kane 1996a).

There were a number of problems with the inhalation studies conducted prior to 1985, which were addressed in later studies (see Section 4.1). Nevertheless, several questions remain regarding respirability, dosing, and sensitivity. Biopersistence of fibers can be affected by the presence of particles in the exposure dose, leading to particle overload. Particle overload is a condition noted primarily from inhalation studies in the rat that occurs when the deposition rate of poorly-soluble, low cytotoxicity particles exceeds the normal macrophage-mediated clearance rate. Clearance mechanisms can become

impaired under high-exposure conditions resulting in chronic alveolar inflammation, fibrosis, and lung tumors. IARC (2002) reported that overload occurs in the rat when 1 to 3 mg of particles are deposited per gram of lung tissue. This condition leads to non-specific lung injury and possibly lung tumors (Hesterberg and Hart 2001, IARC 2002).

Oberdörster (1996) noted two important differences between humans and rats that relate to respiratory tract dosimetry: (1) most of the lung tumors develop in the conducting airways of humans but develop only in the peripheral region in rats; therefore, respirable fibers appear to be more important in the rat; and (2) because of the differences in respiratory physiology, respirable fibers represent very different fractions in humans and rats (see Section 5.1). Therefore, Oberdörster recommended enrichment of the inhaled aerosol with long fibers in order to deposit enough of them into the respiratory tract of the rat. Pertinent questions for inhalation studies of fiber carcinogenicity were also addressed and included the following: (1) should rat respirable or human respirable samples be used, (2) is it possible to test the longer human respirable fibers (*i.e.*, the most potent fibers) in the rat inhalation model, and (3) are chronic inhalation studies in rats sensitive enough to detect lung tumors below the MTD for any fiber type?

The conventional definition of the MTD is *a dose that produces no increased mortality compared with controls, no shortening of life span other than that resulting from tumor development and no more than a 10% weight gain reduction compared with controls* (Kane *et al.* 1996). However, the conventional definition might not be adequate for fiber studies. Muhle *et al.* (1990) introduced the concept of the *maximal functionally tolerated dose* (MFTD) for particulates. The MFTD was defined as the lung burden associated with a two- to four-fold decrease in particle clearance. Other indicators that could be useful in identifying the MTD for fiber inhalation studies include the following: increased lung weight, increased inflammatory parameters, increased target cell proliferation, altered histopathology other than carcinogenicity, impaired lung clearance function, and non-linear fiber retention kinetics (Oberdörster 1996, Greim 2004). Hesterberg *et al.* (1996a) used lung toxicity and particle clearance to estimate the MTD for glass wool and concluded that 30 mg/m^3 (~230 to 300 fibers/cm^3) was an appropriate MTD for MMVF 10 in their chronic inhalation studies (see Section 4.1.1).

Ellouk and Jaurand (1994) noted that for animal models to be relevant to human exposures, inhalation studies require the use of fibers or particles that are respirable in the species tested. However, it may not be possible to increase the respirable dose beyond the MTD for an animal model. Therefore, investigations by the inhalation route should be reserved for respirable fibers, i.e., thin fibers of a diameter allowing lung deposition.

Wardenbach *et al.* (2005) noted that humans are more sensitive to asbestos-induced carcinogenicity by inhalation than rats (see above for a discussion of this opinion and opposing views) and presented arguments in favor of using intraperitoneal injection to test for fiber carcinogenicity. In a comparison of recent chronic rat inhalation studies using special-purpose fibers and insulation wool fibers, differences between the exposure concentrations of these two types of fibers decreased with fiber length and barely existed for fiber lengths > 20 μm (Figure 4-3). However, at every length category examined (total, > 5 μm, > 20μm) special-purpose fibers had a higher concentration of lung fibers (per dry lung weight) as compared with insulation glass wool fibers (Figure 4-4). The special-purpose fibers induced tumors; whereas, the glass wool fibers did not. These results suggested that special-purpose fibers are more respirable than glass wool fibers. Previous studies had shown that almost all of the special-purpose fibers were respirable; however, data were not available on the respirability of insulation glass wool fibers. [Table 4-4 reports data that show that for glass wool fiber exposure concentrations of 3 to 30 mg/m^3, there are 29 to 232 WHO fibers/cm^3. In these studies, these fibers were approximately 81% to 90 % of the total mass of fibers in the exposure aerosol. No lung tumors were detected above control values. These exposure concentrations are in contrast to the crocidolite positve control (10 mg/m^3), which had an exposure concentration of 1,600 WHO fibers/cm^3 and a significant increase in lung tumors.] Because of the low sensitivity of the inhalation model and the possible differences in respirability and outcome in the rat model, the intraperitoneal model was proposed (See below).

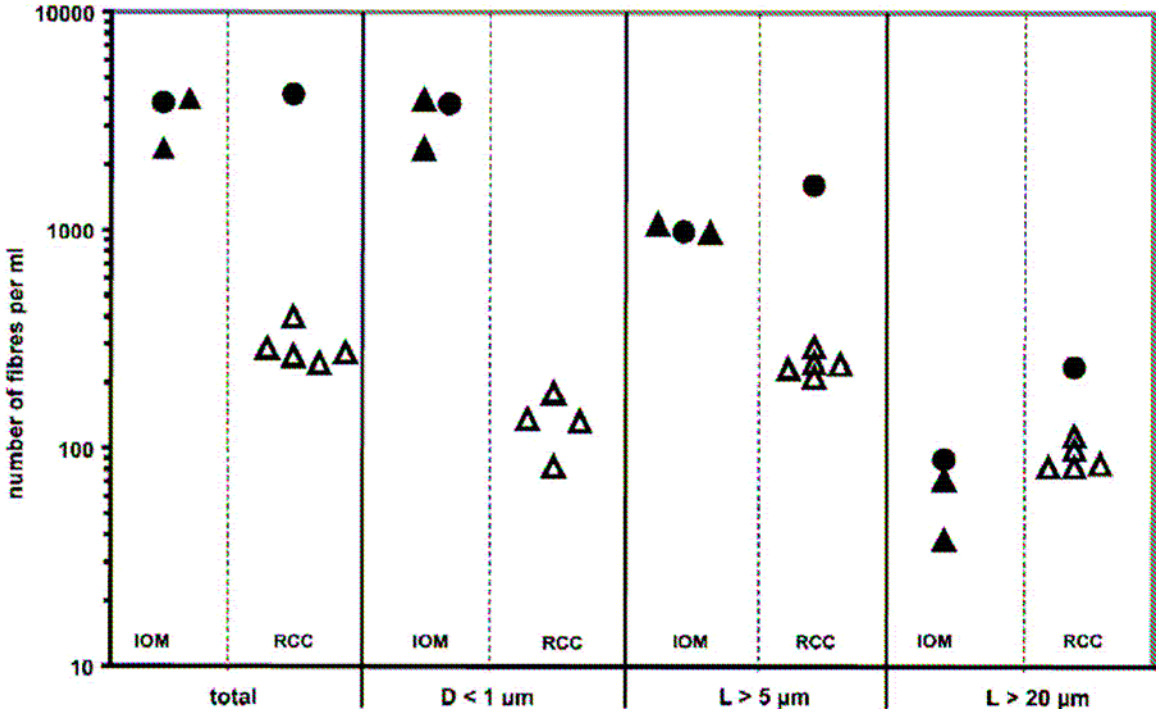

Figure 4-3. Exposure concentration vs. size categories of fibers from rat inhalation studies conducted at two different laboratories

(Research and Consulting Company (RCC, Geneva, Switzerland); Institute of Occupational Medicine (IOM, Edinburgh, Scotland)).Closed symbols-statistically significant induction of lung tumors; open symbols-non-significant for lung tumors. Triangles: MMVFs except RCFs, Circles amphibole asbestos. L=Length, D= Diameter.

Source: Wardenbach *et al*. 2005 (some points estimated from diagrams).

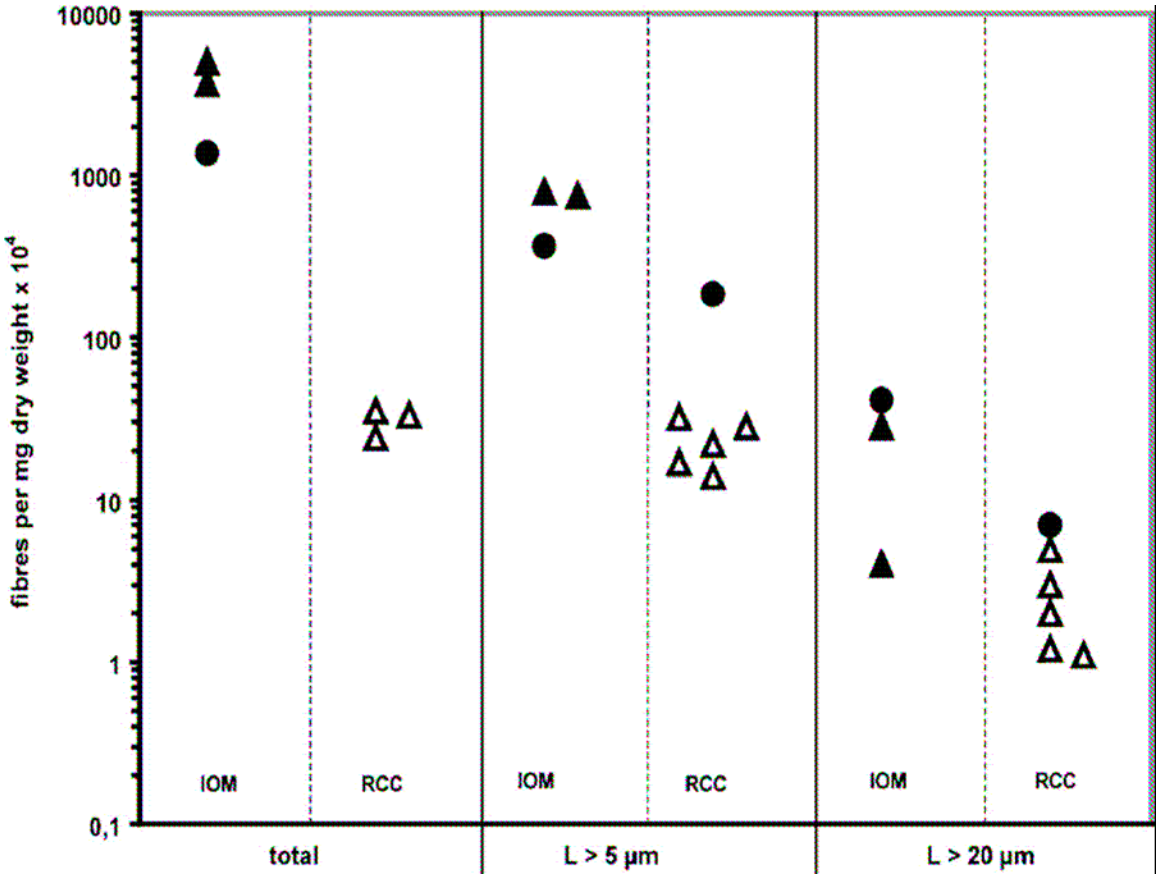

Figure 4-4. Concentration of fibers in lung tissue vs. size categories of fibers from rat inhalation studies conducted at two different laboratories

(Research and Consulting Company (RCC, Geneva, Switzerland); Institute of Occupational Medicine (IOM, Edinburgh, Scotland)) Concentration of fibers is in mg/dry weight of tissue. Closed symbols-statistically significant induction of lung tumors; open symbols-non-significant for lung tumors. Triangles: MMVFs except RCFs, Circles amphibole asbestos. L=Length, D= Diameter.

Source: Wardenbach *et al.* 2005 (some points estimated from diagrams).

Intratracheal instillation

One of the advantages of intratracheal instillation is that selected doses of human respirable fibers can be delivered directly to the lung (Oberdörster 1996). Although the delivered fibers are then subject to the lung's normal defense mechanisms, these mechanisms might be adversely affected if the doses were too high. The primary differences between intratracheal instillation and inhalation studies are the delivery of the entire dose in seconds rather than over several hours, bypassing of the defense mechanisms of the extrathoracic region, and the lack of even distribution of the dose within the lung. Although multiple treatments are generally used, the dosing interval is

typically one week. Therefore, the exposure protocol does not mimic normal human exposure. Careful selection of dose is required because high local doses can cause an acute inflammatory effect (bolus effect) that would likely not occur during inhalation exposure. Oberdörster (1996) concluded that this method was well suited for comparative studies of dose response and toxicity ranking of different fiber types, but a well-conducted multidose asbestos study is needed to validate this method for carcinogenicity assessment.

Intracavity injection

Intracavity injection studies, particularly i.p., are commonly used to evaluate the carcinogenicity of fibers. The primary advantages of these studies are that they are less labor intensive, are easy to perform, and have been successfully used to investigate the carcinogenic potential and potency of fibers (Oberdörster 1996). Repeated injections at weekly intervals over several months have been performed, but most studies used single injections. The disadvantages of intracavity injection studies are similar to those mentioned above for intratracheal instillation studies and include the following: (1) these methods are nonphysiological in that the lung is completely bypassed, (2) the peritoneal and pleural cavities do not have the same defense mechanisms as the lungs and might be overwhelmed following intracavity injections of large doses, and (3) intracavity injection completely circumvents the fiber selection process that occurs during translocation of fibers from the alveolar region of the lung to the pleura (Kane 1996a). Further, the relationship of fiber durability to the incidence of peritoneal tumors needs to be addressed (Ellouk and Jaurand 1994).

Oberdörster (1996) noted the importance of the MTD in intracavity injection studies, as the bolus delivery of fibers to the peritoneal cavity can result in toxicity due to high local doses.

Wartenbach *et al.* (2005) supported the use of the intraperitoneal injection model because the carcinogenic potency of various MMVF can differ by three orders of magnitude. The increased sensitivity of the i.p. route would enable the selection of less potent MMVFs [See Table 4-6 for i.p. doses (in mg) of glass wool fibers (which have a ten-fold dose range) and tumor incidences]. They also stated that there was no evidence that i.p.

injection studies would be biased towards producing false positive results since no mesotheliomas were induced in rats given a high mass of granular silicon carbide dust by i.p. injection.

4.6 IARC evaluations

The IARC (1988) review concluded that there was *sufficient evidence* for the carcinogenicity of glass wool in experimental animals. Later, IARC (2002) evaluated insulation glass wools and special-purpose glass fibers separately as part of a review of man-made vitreous fibers and concluded that there was *limited evidence* in experimental animals for the carcinogenicity of insulation glass wools but *sufficient evidence* in experimental animals for the carcinogenicity of special-purpose glass fibers. The data and findings from these reviews and other publicly available, peer-reviewed carcinogenicity studies in experimental animals were summarized in this section.

4.7 Summary

Numerous studies of various types of commercial insulation glass wools, special-purpose glass fibers, and some experimental fibers have been conducted for carcinogenicity in experimental animals by inhalation, intraperitoneal (i.p.) injection, intrapleural injection, intratracheal instillation, and intrathoracic injection or implantation. Findings from these studies are summarized by fiber types, species, and route of exposure in Table 4-10.

Although all inhalation studies conducted prior to the late 1980s were negative, the results were considered inconclusive because of various study limitations recognized by researchers in the field, including a failure in some studies to produce tumors in positive control groups exposed to asbestos fibers. A series of long-term inhalation studies, which the authors considered to be better designed, were conducted in rats and hamsters in the late 1980s and early 1990s to address the limitations of the earlier studies. Two glass wool fibers (MMVF10 and MMVF11) and two special-purpose fibers (JM100/475 and 104E) were tested in separate studies. Significantly increased incidences of lung carcinomas combined with adenomas occurred in male Wistar rats exposed to 104E microfibers but not to JM100/475 fibers; no significant increases in lung tumors or mesotheliomas were reported for male F344 rats exposed to MMVF10, or MMVF11. In

the most recent inhalation study in male hamsters, mesothelioma was observed in one of 83 animals exposed to JM100/475 glass fibers for 78 weeks.

Significantly increased incidences of peritoneal tumors (primarily mesothelioma) were reported in almost all i.p. injection studies in rats using different type of fibers including insulation fibers such as MMVF10 and MMVF11 and special-purpose fibers such as JM475 (various diameters), M753, and E glass. However, no tumors were observed in some studies testing experimental fibers that have low biodurability. In most cases, tumor incidences were similar to those seen in the asbestos treatment groups. In addition, increased incidences of pleural sarcomas occurred in rats following intrathoracic implantation of some glass fibers (depending on the fiber dimensions) but not others. Increased incidences of neoplasms (mesothelioma, pleural sarcoma, and lung carcinoma) were observed in some intrapleural or intratracheal instillation studies in rats exposed to JM100 or JM104 microfibers and in intratracheal instillation studies in hamsters exposed to JM104 microfibers. No tumors were reported following intrapleural or intratracheal instillation of glass wool in mice, guinea-pigs, or rabbits.

A number of studies, including both intrathoracic implantation and intraperitoneal injection of fibers, have been conducted with the intent of comparing fibers with different characteristics, such as differing fiber dimensions and biopersistence/durability. The earliest of these studies by Stanton and co-workers using intrathoracic implantation of glass fibers and other natural and synthetic fibers led the authors to conclude that fiber dimensions and durability were important in determining the tumorigenicity of the material. Later studies using intraperitoneal injection reached similar conclusions in many cases, but some data suggest that the relationship might not be completely defined by those fiber characteristics.

Table 4-10. Summary of carcinogenicity studies of glass wool fibers in experimental animals.

Fiber type/source	Exposure route					
	Species	Inhalation[a]	Intraperitoneal	Intratracheal	Intrathoracic	Intrapleural
Insulation wool	Rat (not specified)			–		
	Wistar		+			
	Sprague-Dawley					–
	Osborne-Mendel				±	
	F344	–	–			
	Syrian golden hamster	–		–		
	Guinea pigs			–		
	BALB/c mice					–
	Rabbits			–		
475 glass	Wistar	–	+	+		±
	Sprague-Dawley		+			+
	Osborne-Mendel		+	–		
	F344		–			
	Syrian golden hamster	–		±		
E glass	Wistar	+	+			
753 glass	Wistar		+			
Experimental fibers	Wistar		±			

[a] – = negative studies; + = positive studies; ± = both positive and negative studies.

5 Other Relevant Data

This section discusses the deposition, clearance, and retention of glass fibers (Section 5.1); their durability and biopersistence (Section 5.2); toxicity (Section 5.3), genetic and related effects (Section 5.4), and the mechanisms of fiber-induced carcinogenesis (Section 5.5). Much of what is known about fiber carcinogenicity was discovered in studies with asbestos, and the general principles are relevant for glass fibers. Therefore, this section includes some discussion of asbestos carcinogenicity with comparisons to glass fibers.

5.1 Respirability, deposition, clearance, and retention

Two important concepts relating to exposure to airborne particulates are *inhalability* and *respirability*. Inhalability is the ratio of the particle concentration in the inhaled air to that in the ambient air and decreases with increasing particle size. Larger particles settle out of the air faster and are more readily filtered in the extrathoracic region. Respirability refers to the relative amount of airborne particles reaching the alveolar region of the lung and generally increases with decreasing particle size (Hesterberg and Hart 2001). Variations in fiber density, length, and diameter can be normalized using the equivalent aerodynamic diameter (D_A). D_A is expressed as the diameter of a spherical particle that has the same terminal settling velocity in still air as the fiber and is calculated as follows: $D_A = 1.3p^{1/2}d^{5/6}L^{1/6}$ (where D_A = aerodynamic diameter, p = density, d = diameter, L = length) (Hesterberg and Hart 2001). In humans, fibers with a $D_A < 1$ μm are 100% respirable, fibers with a D_A of about 4 μm are 50% respirable, and fibers with a D_A of 9 to 10 μm are non-respirable (Hesterberg and Hart 2001). Morgan *et al.* (1980) reported that respirability in the rat peaked at an aerodynamic diameter (D_A) of approximately 2 μm and decreased markedly between 2 and 3 μm, with $D_A < 6$ μm being the limit of respirability (no fiber alveolar deposition). Dai and Yu (1998) calculated respirability of inhaled fibers in rats based on deposition models. They reported the limit of respirability in the rat at $D_A > 3.5$ μm and aspect ratios > 10, and noted that there was appreciable fiber deposition in humans at this fiber size. Respirable fibers can cause adverse effects in the lung such as pulmonary inflammation, cell proliferation, pulmonary fibrosis (collagen deposition) and neoplasia (Oberdörster 2000). Fibers that are inhalable but non-respirable

can deposit in the extrathoracic and tracheobronchial regions and can cause adverse effects including acute nasal effects, chronic inflammation, and bronchogenic carcinoma (Churg 1988).

There are marked species differences in the amount of fibers retained in the airway for a given exposure concentration with both anatomic and physiologic factors influencing the dose retained (IARC 2002, Oberdörster 2000). It is important to note that exposure concentration in ambient air is not equivalent to the dose deposited in the lung. Deposition is the actual dose deposited in the lung from the inspired air as a result of inelastic encounters of the particles with the respiratory epithelium and is influenced by the anatomy and physiology of the airway, respiratory rate, and physical properties of the fiber. Once deposited, fibers can be removed or cleared from the respiratory tract. Clearance is defined as the amount of fibers eliminated (cleared) from the lung over a time period and is influenced by both the physical properties of the fiber and the physiologic response of the host. Retention is defined as the dose retained within the lung and is equal to deposition minus the amount cleared. This section briefly reviews some of the primary concepts relating to deposition, clearance, and retention of fibers in the respiratory tract.

There are three general regions of the respiratory tract where inhaled particles deposit. These are the extrathoracic region (mouth, nose, pharynx, and larynx), the tracheobronchial region (trachea, bronchi, and bronchioles), and the alveolar-interstitial region (respiratory bronchioles, alveolar ducts, alveoli, and pulmonary interstitium) (IARC 2002).

5.1.1 Deposition

Respirability determines the concentration of particles in the air reaching the alveoli, whereas, deposition is the actual dose deposited in the lung. In humans, 40% to 80% of fibers with $D_A < 1$ μm that are inhaled into the lower lung are not deposited and are subsequently exhaled from the lung (Hesterberg and Hart 2001). Deposition is a function of the physical characteristics of the particle, such as size, shape, and density, and the anatomical and physiological parameters of the respiratory tract. Distribution of fibers within an alveolus is dependent on alveolar geometry and the composition and physical

properties of alveolar fluid. Alveolar fluid consists of an aqueous layer over the pulmonary epithelium covered by a surfactant layer at the air-liquid interface (Geiser *et al.* 2003).

Fibers deposit in the respiratory tract by impaction, sedimentation, diffusion, and interception (see Glossary for definitions). All four deposition mechanisms occur in humans and experimental animals. Impaction and sedimentation are most effective for particles with aerodynamic diameters of 0.5 to 1 μm. Deposition due to aerodynamic behaviour becomes less important as particle size decreases below 1 μm, and for particles with aerodynamic diameters less that 0.5 μm, deposition is mainly determined by diffusional displacement induced by Brownian motion. Interception is more important for deposition of fibrous particles than of spherical particles because it occurs when one end of the particle touches the epithelium of the airway (Bernstein *et al.* 2005).

Although mechanisms of deposition are similar between humans and experimental animals, there are some important interspecies differences that can influence fiber deposition (IARC 2002, Maxim and McConnell 2001):

- Rats are obligate nose breathers; humans can breathe through the mouth and nose,
- Nasal turbinates in rodents are more complex than in humans and filter fibers more efficiently; this, along with other differences in size and physiology, results in more and larger fibers depositing in human lung than in the rodent,
- The conducting airways in humans are dichotomous and symmetrical resulting in greater impaction of fibers at branch points while in rodents they are monopodial and asymmetrical favoring a more uniform airflow resulting in distal deposition of fibers,
- In humans, the deposition fraction in the extrathoracic and tracheobronchial regions increases with workload (minute ventilation), and deposition increases when switching from nose to mouth breathing.

Dai and Yu (1998) studied alveolar deposition in rodents and humans and found that aerodynamic fiber diameters between 1 and 2 μm result in peak lung deposition in

rodents and humans and that increasing the aspect ratio (ratio of fiber length to fiber diameter) of the fibers decreases the peak deposition. Further, alveolar deposition in rodents does not occur when D_A is greater than 3.5 μm and the aspect ratio is greater than 10; whereas, considerable alveolar deposition occurs in humans with particles having aerodynamic diameters approaching 5 μm.

5.1.2 Clearance

Clearance mechanisms vary from region to region within the respiratory tract. Ciliary movement in the extrathoracic region clears deposited particles cranially, primarily towards the pharynx where they may be swallowed or cleared by coughing. Particles within the nasal cavity may be cleared by nose-blowing or sneezing. Ciliated epithelial cells line the airway from the pharynx caudally to the terminal (respiratory) bronchioles and clear the airway by moving particles, cells, and fluids back to the pharynx where they can be swallowed or coughed out. This system, known as the mucociliary escalator, is an important clearance mechanism for the tracheobronchial region. Mucociliary clearance usually takes less than 24 hours. Airway macrophages can clear many particles through phagocytosis and subsequent mucociliary clearance. Phagocytosis is the primary clearance mechanism in the alveolar region and is slower than clearance from other regions of the airway. The presence of fibers on the lung epithelium stimulates the release of chemotactic factors that attract alveolar macrophages, neutrophils, and other cells involved in inflammation, and these activated cells also release chemotactic and other factors (Wilson and Wynn 2009). Fiber length is known to be an important factor for phagocytosis, and there are species differences in alveolar macrophage size and number. Fibers that are too long to be fully phagocytized and too durable to be broken down may remain in the alveolar region with macrophages attached to the fibers (a phenomenon called “frustrated macrophages”) or can translocate to interstitial and pleural sites (Oberdörster 1996). In general, small particles in the alveoli are phagocytized, but they have also been found in alveolar capillaries (Geiser *et al.* 2003).

The clearance of fibers in the lung over time has been studied by Bernstein *et al.* (2001a). Tracking percent fiber retention in the lung over time (days following cessation of exposure) resulted in a bi-phasic extinction curve. The rate of fiber clearance (slope of

the line) is initially fast and then markedly decreases resulting in a bi-exponential curve. The fast clearance phase is proposed to represent clearance of short fibers from either the tracheobronchial or alveolar regions and clearance of long fibers (> 20 μm) from the tracheobronchial region. The slow clearance phase is proposed to describe dissolution of shorter fibers that have accumulated in microgranulomas or the bronchial-associated lymphoid tissue and lymph nodes, or dissolution of fibers that were too long to be phagocytized by macrophages. Because of the importance of alveolar macrophages, species differences in macrophage size and number may affect fiber clearance. Macrophages in humans have an average diameter of about 21 μm compared with about 13 to 14 μm in rats and hamsters (Hesterberg and Hart 2001).

Zeidler-Erdely *et al.* (2006) investigated the influence of JM100 fiber length on lactate dehydrogenase release in primary cultures of human alveolar macrophages. Human macrophages completely engulfed glass fibers up to 20 μm in length, with no evidence of incomplete phagocytosis or length-dependent toxicity. Whereas, in a study of cytotoxicity using Code 100 glass fibers and rat alveolar macrophages (Blake *et al.* 1998), evidence of a length-related toxicity was seen with fibers of 17 and 33 μm. (see Section 5.3.3, Cytotoxicity, for study details.)

Differences in the phagocytic response of rat and hamster alveolar macrophages to SVFs have been investigated by Dörger *et al*. (2000). Alveolar macrophages were obtained by bronchoalveolar lavage, and macrophage-enriched cell cultures were exposed to either MMVF10 (glass wool, median length 16.3 μm) or MMVF21 (rock wool, median length 19.4 μm) for 20 hours. The phagocytic response was video recorded. Rat macrophages had a significantly ($P < 0.05$) greater percentage of cells with partial phagocytosis than hamster macrophages for MMVF10 (27% vs. 2%) and MMVF21 (30% vs. 1%). Also, a higher percentage of hamster macrophages completely phagocytized both types of fibers (18% vs. 9% for MMVF10 and 33% vs. 16% for MMVF21). After a 2-hour exposure to the fibers super oxide anion production was also measured by a cytochrome c reduction assay. Rat alveolar macrophages released significantly higher amounts of super oxide anion than hamster macrophages with MMVF21 exposure, but not with MMVF10 exposure. The authors concluded that there were species differences in the phagocytic

response that could result in more efficient clearance of inhaled fibers from hamster lung than from rat lung.

Using the same methods and fibers, Dörger *et al*. (2001) also compared super oxide anion production and phagocytic response of rat alveolar macrophages to rat peritoneal macrophages. Alveolar macrophages had a greater number of partly incorporated fibers (41% vs. 10% for MMVF10; 34% vs. 12% for MMVF21) and had a lower percentage of fiber-free macrophages (9% vs. 50% for MMVF10, 9% vs. 29% for MMVF21) than peritoneal macrophages. Alveolar macrophages produced significantly greater amounts of superoxide anion than peritoneal macrophages when exposed to MMVF21 (approx. 150 vs. 10 nmol/mg protein per 2 hours), but exposure of alveolar or peritoneal macrophages to MMVF10 did not result in production of superoxide anions. The authors concluded that these data are consistent with a higher biopersistence of mineral fibers in the peritoneal cavity as compared with the lung.

5.1.3 Retention

Retention is defined as deposition minus clearance. Chemical composition, fiber size distribution, number of fibers in the lung, and time since the last exposure are important factors. Based on the experimental data, two possible mechanisms have been proposed to explain the length-related patterns of fiber retention (Oberdörster 2002). Short fibers are expected to be efficiently phagocytized by the alveolar macrophages and transported from the alveoli to bronchioles where they are cleared by the mucociliary escalator. Long fibers are resistant to phagocytosis but may be subject to dissolution or transverse breakage. As the long fibers break, the population of short fibers is increased; therefore, the population of long fibers typically decreases faster than the population of short fibers for nondurable types of fibers (see the following section). If long fibers are resistant to transverse breakage or dissolution (*e.g.*, asbestos), they are retained. The second possible mechanism is based on differences in the intracellular and extracellular compartments of the lung. Long fibers tend to remain in the extracellular compartment because they cannot be completely phagocytized by macrophages. The extracellular compartment is at near-neutral pH, whereas, phagocytosis by alveolar macrophages exposes the fibers to the

acidic pH and digestive factors within the phagolysosomes. Thus, the solubility of long fibers at neutral pH would be an important factor in dissolution of the fiber.

A limited number of studies is available regarding retention of fibers in humans; however, the average overall retention half-time for poorly soluble fibers has been reported to be hundreds of days. In one study (McDonald *et al.* 1990), which used a subset of the Marsh *et al.* cohort, analytical transmission electron microscopy was used to determine fiber retention in lung tissue. The selected population consisted of 112 MMVF workers (101 glass wool workers and 11 rock or slag wool workers) that had died between 1952 and 1979 with tissue available from autopsies; the unexposed group consisted of 112 autopsies from the same hospital. There was no significant difference in retention of fibers in the 112 exposed workers as compared with the unexposed group. The exposed workers had a mean exposure duration of 11 years and a mean elapsed time since last exposure of 12 years. Fibers were detected in 29 of the 112 production workers compared with 28 of 112 in the unexposed group. Fiber numbers detected in the exposed workers and the unexposed group were similar to those found after environmental exposure. However, 10 of the 112 exposed workers and 2 of the 112 unexposed group had more than 1 million asbestos fibers/g dry lung tissue. The authors concluded that either the synthetic fibers disappeared from the lung in less than 12 years, or the exposed workers did not inhale enough respirable fibers to show a difference from controls; alternatively, fixative fluids might have altered some retained fibers in the lung.

5.2 Biodurability and biopersistence of glass fibers

This section reviews several studies that illustrate the differences in biodurability and biopersistence among fiber types and the various ways these properties are measured. The relationship between fiber biopersistence and pathogenicity in experimental animal models and humans is also discussed.

5.2.1 Definitions

Biodurability describes the rate of removal of a fiber from the lungs by dissolution or disintegration, the latter due to partial dissolution. It is assumed that biodurability is similar in rats and humans since the ionic milieu in the lung is also relatively similar. On the other hand, biopersistence also includes the removal of fibers from the lung by

physical clearance of entire fibers, *e.g.*, by ciliary or macrophage-mediated clearance. Therefore, biopersistence is equal to biodurability plus physiological clearance and refers to the capacity of a fiber to persist and to conserve its chemical and physical features over time in the lung (Hesterberg and Hart 2001).

5.2.2 Fiber dissolution

Physico-chemical processes can act on fibers in the lung resulting in chemical dissolution, leaching, and mechanical breaking (IARC 2002). Dissolution occurs when water molecules attack the surface of the fiber. For many SVFs, certain components dissolve more rapidly than others (leaching). Leaching results in changes in fiber composition over time. As the zones of leached-out, lower-density material expand, fiber weakness (*e.g.*, fractures, peeling, and pitting) and breakage occur. Therefore, chemical composition and surface reactivity of the fiber affect its dissolution rate. Maxim *et al.* (2006) reported that fluorine and oxides of boron, magnesium, calcium, sodium, and barium increase the dissolution rate, while aluminum oxide decreases the dissolution rate of borosilicate glass fibers.

Experimental dissolution rates of various fibers have been studied in a number of *in vitro* and *in vivo* systems. Cell-free systems typically use balanced salt solutions to simulate lung fluids and are conducted at near neutral pH (to simulate the pH of extracellular fluid) or at a pH of 4.5 (to simulate the pH of the phagolysosomes of macrophages). Results with cell-culture studies are generally consistent with results from the cell-free systems, but dissolution of glass wool is faster in cell-free systems. Reported *in vitro* dissolution rate constants in cell-free systems at neutral pH are < 1 ng/cm^2 per hour for crocidolite, 8 to 12 ng/cm^2 per hour for E-glass and 475 glass, and 100 to 300 ng/cm^2 per hour for building insulation glass wools (Zoitos *et al.* 1997). Although experimental dissolution rates for glass fibers show considerable variability (up to a 30-fold range), they generally show some correlation with clearance rates of long fibers from the lung in short-term biopersistence studies (see next section). Therefore, *in vitro* dissolution tests have been used to screen for toxicity.

Luoto *et al.* (1995b, 1994) studied the effect of fiber length on the dissolution of commercial glass wool and rock wool fibers in cell-culture medium with and without rat

alveolar macrophages present. Atomic absorption spectroscopy was used to determine the amount of iron, aluminum, or silicon remaining in original and tested fibers. More iron and aluminum dissolved from fibers in culture with macrophages, while more silicon was dissolved from fibers in culture medium without cells. Further, they found that glass wool fibers (MMVF10, MMVF11) dissolved more readily at pH 7 in culture medium alone than rock wool fibers; whereas, rock wool fibers dissolved more readily when macrophages were present in the culture medium (Luoto *et al.* 1995a). These authors concluded that the intracellular and the extracellular dissolution of the fibers differ, and that cell-culture systems were preferable to cell-free systems for assessing fiber durability and dissolution.

Nguea *et al.* (2008) proposed an *in vitro* test for fiber degradation using a human monocytic cell line (U-937). Crocidolite fibers (asbestos), glass wool fibers (CM44) and rock wool fibers (HDN) were tested. After a 24-hour incubation of U-937 cells with each of the fibers, phagocytosis was observed; however, dissolution of the fibers (as observed by scanning electron microscopy) did not occur. Degradation of CM44 and HDN fibers occurred only with activation of the monocytes with *E. coli* bacteria, *E. coli* culture media, IL-6, or TNF-alpha, but not with lipopolysaccharide (LPS), *B. subtilis*, *S. aureus*, or heat-inactivated *E. coli*. Asbestos fibers did not degrade in the presence of *E. coli.* The pattern of HDN fiber degradation observed *in vitro* was in accord with that observed in rats after a one-month intratracheal exposure.

In general, biodurability of various fibers in the lung have been ranked as follows: glass fibers < refractory ceramic fibers < chrysotile asbestos < amphibole asbestos (Collier *et al.* 1994). Collier *et al.* (1994, 1995) compared the durability of an experimental glass fiber (X7753) of uniform diameter (2 μm) by injecting fibers into the peritoneal cavity and by intratracheal instillation to the lung of female Fischer rats. Scatter plots of fiber diameter vs. fiber length were produced to estimate the injected fiber size distribution and the size distribution for the fibers recovered 150 days after either intratracheal instillation or intraperitoneal injection. After 150 days of exposure, fibers were recovered from the tissues by lavage. Fiber diameters by both routes of exposure had decreased; whereas, there was an apparently greater decrease in fiber length by the intratracheal route of

exposure. [These conclusions are based on a qualitative assessment of the scatterplots by the authors.] Peak diameters of fibers > 20 μm and < 20 μm in length were plotted against days after administration by both routes. The diameters of long fibers (> 20 μm) declined from 2 μm to below 0.4 μm by 50 days after administration by the intratracheal instillation route, but remained above 1 μm for intraperitoneal exposure. Diameters of short fibers (< 20 μm) remained above 1 μm for both injection routes [diameters estimated from graphs]. Their results suggested that dissolution rates of long fibers were slower in the peritoneal cavity compared with the lung. In the peritoneal cavity, diameters of both short and long fibers declined at a rate similar to that of short fibers in the lung. Doses greater than 1.5 mg in the peritoneal cavity resulted in clumps of fibers (nodules) that were either free in the cavity or bound to peritoneal organs and were associated with classic foreign body reactions.

5.2.3 Biopersistence studies

Yu *et al.* (1998) evaluated the biopersistence of MMVF10 (glass wool), MMVF11 (glass wool), MMVF21 (rock wool) and MMVF22 (slag wool) and developed a clearance model in the rat lung using experimental data from short-term, nose-only inhalation biopersistence studies. Crocidolite asbestos was used as a positive control. Their model accounted for differential mechanical clearance by alveolar macrophages, *in vivo* dissolution of fibers, and breakage of long fibers. The *in vitro* dissolution rate was correlated with the *in vivo* dissolution rate, although the *in vivo* rate was much lower. Fiber breakage was related to dissolution. The breakage rate of the more soluble fibers was higher. MMVF10 had the highest dissolution and breakage rate followed closely by MMVF11 and MMVF22. Because crocidolite fibers are highly durable, the authors assumed that removal was by macrophage-mediated mechanical clearance alone. Different half-times were calculated for different fiber lengths. For crocidolite fibers shorter than 5 μm, mechanical clearance was about the same as for nonfibrous particles but decreased with fiber length. For crocidolite fibers longer than 20 μm, the average mechanical clearance rate was 0.001 (1/day) and corresponds to a half-time of 693 days.

A different approach for the calculation of half-times was used by Bernstein *et al.* (1996). The authors examined the biopersistence of nine SVF in the rat. These included

MMVF11, three experimental glass wools (including B-01-0.9), one commercial stone wool, and four experimental stone wools. Groups of 56 male F344 rats were exposed (nose only) to a well-defined rat-respirable aerosol (mean diameter < 1 μm) at a concentration of 30 mg/m^3 for 6 hours per day for 5 days. Groups of 8 animals were sacrificed at 1 hour, 1 day, 5 days, and 4 weeks following the last day of exposure and at 13, 26, or 52 weeks following the first day of exposure. Clearance, when modelled with a single exponential curve, did not provide a good fit to the experimental data for many of the fibers. Both a fast-clearance phase and a slow-clearance phase were observed for many of the fibers; therefore, a weighted clearance half-time ($WT_{½}$) was calculated. This method provided a much better fit to the data. The $WT_{½}$ for World Health Organization (WHO) fibers[2] was 28 days for MMVF11 and ranged from 11 to 15 days for the three experimental glass wools. WHO fiber clearance was shown to represent clearance of shorter fibers (5 to 20 μm) but was not a good indicator of the clearance of the more biologically relevant longer fibers (> 20 μm). The $WT_{½}$ for the longer fibers was 13 days for MMVF11 and only 2 to 4 days for the experimental glass wools, indicating that clearance of long glass fibers was rapid due to dissolution and breakage. For comparison, the $WT_{½}$ for crocidolite fibers longer than 20 μm was 536 days. [This approach uses the fraction of the short half-time which does not contribute to fiber accumulation in the lungs. Some authors have suggested that only the slow phase of the half-time should be used (Wardenbach *et al.* 2000).]

Hesterberg *et al.* (1998) used the rat inhalation model to compare biopersistence of long amosite with five SVFs. The test fibers included two special-purpose fibers, MMVF32 (E glass) and MMVF33 (475 glass). Fischer rats were exposed for 6 hours/day for 5 days and followed for one year. Mass concentrations were adjusted to achieve target concentrations of 150 fibers/cm^3 > 20 μm. Groups of 5 to 8 rats were sacrificed at 9 post-exposure time points (1, 2, 7, 14, 30, 60, 90, 180, and 365 days) to evaluate lung fiber burdens, dimensions, and morphology. Lung deposition of fibers > 20 μm was similar for

[2] WHO fibers are respirable fibers with lengths greater than 5 μm, diameters less than 3 μm, and aspect ratios (ratio of fiber length to diameter) ≥ 3:1 ATSDR. 2004. *Toxicological Profile for Synthetic Vitreous Fibers*. U.S. Department of Health and Human services, Agency for Toxic Substances and Disease Registry. 332 pp. .

amosite and the five SVFs, while deposition of WHO fibers was more variable. The authors used a two-pool first-order kinetic model to describe removal of fibers from the lung. Lung burdens for all six fibers were reduced about 35% during the first 90 days compared with day 1 levels. However, during the subsequent slower clearance phase (~275 days), the number of long amosite fibers was 80% of the 90-day value while the number of glass fibers was about 25% of the 90-day value. For amosite fibers > 20 μm the half-times of the fast pool and slow pool were 20 and 1,160 days, respectively, while the $WT_{½}$ was 418 days. For MMVF32 and MMVF33, the half-times were, respectively, 7 and 5 days (fast pool), 179 and 155 days (slow pool), and 79 and 49 days ($WT_{½}$). Amosite fibers did not show any surface deterioration during the 365 days of lung residence while slight surface etching was noted for the glass fibers. The authors noted that in this study and previous studies, between 20% and 60% of long fibers typically clear from the lung during the first two weeks regardless of the dissolution rate of the fiber. This rapid removal indicates that these fibers likely deposit in the upper airways and are cleared by ciliary action. The authors noted that the half-times for the slow pool suggest that glass fibers were subject to dissolution and transverse breakage during lung residence while amosite was not.

5.3 Studies of fiber characteristics and tumorigenicity

5.3.1 Intrathoracic and intraperitoneal studies

Stanton *et al.* (1977, 1981) conducted studies with experiments testing the tumorigenicity of 22 glass fiber preparations, including 18 borosilicate glass fibers, 13 samples of crocidolite (crocid 1-13), 8 samples of aluminum oxide whiskers (alumin 1-8), 7 talcs (talc 1-7), 7 dawsonites (dawson 1-7), 4 wollastonites (wollaston 1-4, 2 tremolites (tremolite 1, 2), 2 attapulgites (attapul 1, 2), 2 halloysites (halloy 1, 2), 2 crystals of silicon carbide and potassium titanate (titanate 1, 2), and 1 crystal of nickel titanate (titanate 3) in the same pleural implantation model. [The results for glass fibers were reported in Section 4, and all results are summarized here.] The tumor incidences and percent tumor probabilities, and common log of the fibers/μg with < 0.25 μm diameter and > 8 μm length are shown in Table 5-1A. Based on induction of significant numbers of pleural sarcomas by fine, durable fibers of chrysotile, crocidolite, amosite, tremolite,

glass, attapulgite, dawsonite, aluminum oxide, silicon carbide, and potassium titanate, Stanton *et al.* concluded that "the carcinogenicity of fibers depends on dimension and durability rather than on physicochemical properties."

Stanton *et al.* (1981) examined 22 glass fiber types (including the 17 fibers tested in the 1977 paper) along with 50 natural and synthetic fibers not tested in the earlier study and reported incidences of pleural sarcomas in various control groups. These included untreated controls (3 of 488), noncarcinogenic pulmonary implants (9 of 432), and noncarcinogenic pleural implants (17 of 598). The authors reported a combined incidence of pleural sarcomas in all control groups of 7.7% (29 of 1,518) based on the life-table method. Tumor incidences in the individual experiments that exceeded 30% were considered significantly different from the combined controls. The authors reported that the incidence of malignant mesenchymal neoplasms correlated with fiber dimensions. The correlation coefficient (r^2) was 0.8 for fibers < 0.25 μm in diameter and > 8 μm in length, but high correlations also were noted in categories with diameters < 1.5 μm and lengths > 4 μm (r^2 = 0.45 to 0.68). The authors also suggested that their experiments could simply be measuring the efficiency of phagocytosis of fibers of different dimensions since short and large-diameter fibers were avidly phagocytosed, while long, thin fibers showed negligible phagocytosis.

After the studies by Stanton and co-workers, most investigators have tested fibers by intraperitoneal injection. Pott *et al.* (1974) compared glass fibers (average diameter of 0.5 μm) with chrysotile, gypsum, nemalite, and palygorscite (Table 5-1B). Based on their results they suggested that fibers less than 10 μm in length could still be carcinogenic. Similarly, they proposed that carcinogenicity could not be limited to fibers with diameter less than 0.5 μm based on the size distribution of fibers in their sample.

Pott *et al.* (1987) reported results from 15 different experiments with approximately 50 fibrous dusts prepared from synthetic and naturally occurring fibers. Experiments 1 through 13 and experiment 15 are summarized in Table 5-1C. (Experiment 14 involved i.p. injections of cadmium and nickel compounds and is not summarized here.) The first 13 experiments had been completed before the publication was prepared, but experiment

15 was still in progress and results were reported through 28 months of observation with some rats in each group still living. Rats were reported as tumor bearing if they were diagnosed with either sarcoma, mesothelioma, or carcinoma of the abdominal cavity, but the authors noted that only a few carcinomas were found, and the three tumor types could not always be differentiated histologically with certainty. The overall conclusion by Pott *et al.* was that length and durability of fibers are significant determinants of carcinogenic potency; however, they pointed out that relatively thick rock and ceramic fibers were "unexpectedly strong" as carcinogens. They did recommend re-measuring several of the fiber samples tested to confirm the relationship between fiber dimensions and carcinogenic effects.

Pott *et al.* (1989) (Table 5-1D) tested 104/475 glass fibers by i.p. injection to female Wistar rats along with 10 other fibrous dusts (and 3 granular dusts not reported here). The authors expressed concern about their ability to compare the dose-response relationship between asbestos fibers and man-made mineral fibers because of uncertainty about the number of fibers in each size category, their durability, and their surface properties. They did point out that actinolite and 104/475 glass fibers had similar size distributions based on the available data and both fibers were durable in rats; however, the number of fibers that induced tumors at approximately a 60% rate was much greater for the glass fibers than for the actinolite fibers. They also found high tumor incidences for the relatively thick basalt fibers and one of the ceramic fibers (Fiberfrax) even though the number of fibers injected per rat was smaller for these fiber types than for the glass fibers. Further, the number of fibers longer than 5 μm was similar in 0.25 mg of actinolite and 75 mg of basalt fibers, and these preparations resulted in similar tumor incidences (56% for actinolite and 57% for basalt). The authors suggested that the carcinogenic potency of the fibers did not decrease with increasing diameter as would have been expected based on earlier publications, and they proposed that either the percentage of very long (> 20 μm) fibers in the two preparations or some unknown surface properties might explain the unexpected results.

Pott *et al.* (1991) (Table 5-1E injected female Wistar rats with 3 different glass fibers with different half-lives *in vivo*. The mean half-lives ranged from 38 days for B-2 glass

wool to 107 days for B-1 glass wool and 238 days for B-3 glass wool. Pott *et al.* noted that only the most durable of the fibers caused tumors. Both the dose and length of the fibers were varied, with fibers designated as either K (kurz, German for short), M (medium), or L (lange, German for long). In the additional experiments reported in Table 5-1E, Pott *et al.* injected a number of different fibrous dusts i.p. They summarized the main results of these experiments for glass fibers as demonstrating that slightly durable glass fibers (B-1 and B-2) did not induce a carcinogenic effect at the doses and fiber sizes tested, which included up to 5.80×10^9 B-2 glass fibers with median length of 6 μm and median diameter of 0.51 μm.

They illustrated the relationship between fibers with long half-life that induced tumors compared with fibers with short half-life that were not carcinogenic after i.p. injection in Figure 5-1.

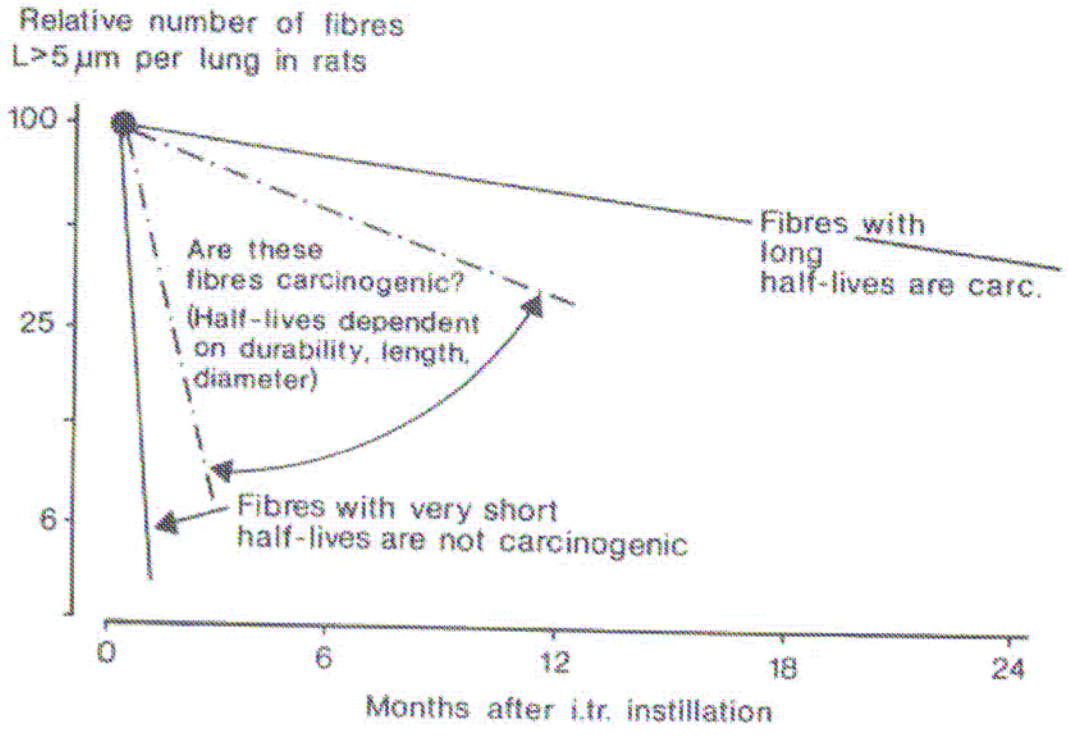

Figure 5-1. Diagram depicting relative difference in fiber half-lives and carcinogenicity

Data shown are relative percentage of fibers > 5 μm long vs. time after intratracheal instillation.

Source**:** Pott *et al.* 1991.

Pott *et al.* also plotted the dose-response relationship between fiber types and percent tumor incidence as shown below in Figure 5-2. They noted that the regression lines for the amphibole fibers (actinolite and crocidolite) differed in dose by a factor of about 20 compared with the regression line for the 6 different glass fibers tested, but they did not have an explanation for the difference.

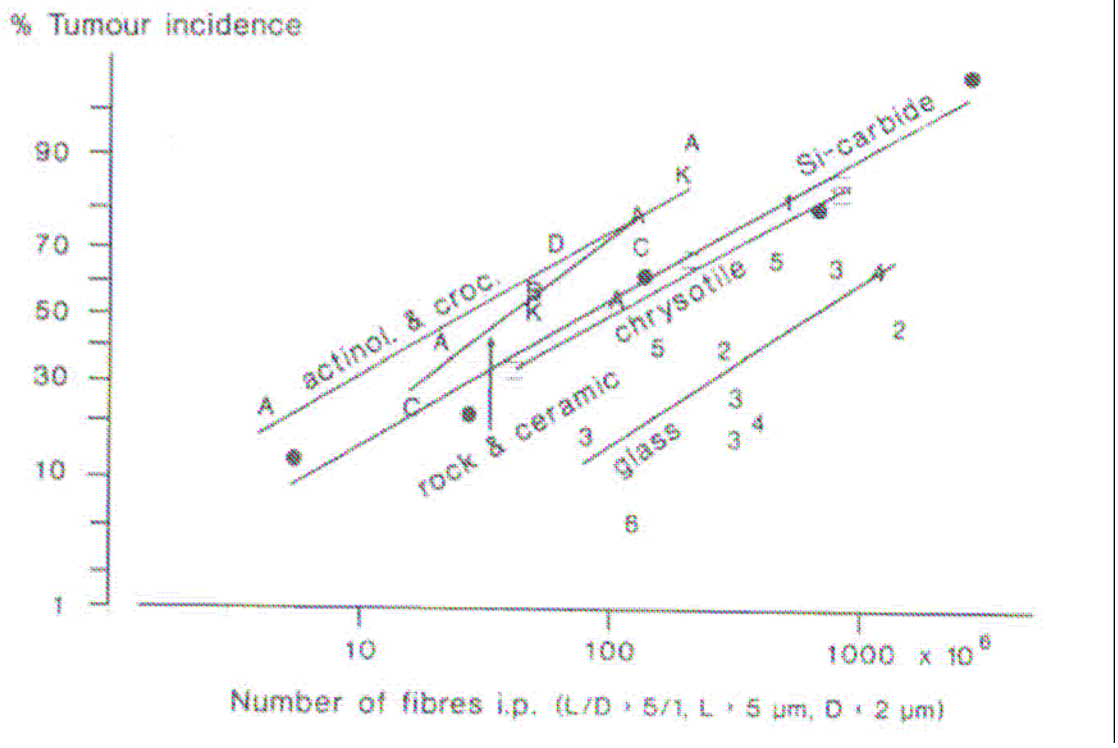

Figure 5-2. Exposure dose by i.p. injection of different fiber types and percent tumor incidence

A=actinolite, K=crocidolite, B=basalt, D=diabase, C=ceramic (2 types); open squares = chrysotile, closed circles = silicon carbide, 1-6 = glass microfibers: 1-3 Manville; 1 = M 104/E, 2 = M 100/475, 3 = M 104/475; 4-6 Bayer; 4 = B 3K, 5 = B 3L, 6 = M 106.
Source**:** Pott *et al.* 1991.

Roller *et al.* (1996) (Table 5-1F) conducted a study designed to examine the dose-response relationship for fiber types of different dimensions and *in vivo* durabilities. The relationships were discussed in Roller *et al.* (1997). The fibers were divided into groups of relatively long, thick fibers (aspect ratio > 5:1, median length 8 to 17 µm, median

diameter 0.7 to 1.2 μm) and short, thin fibers (aspect ratio > 5:1, median length 2 to 4 μm, median diameter 0.2–0.5 μm). The long, thick fibers included the following: Glass fibers B-09-0.9, B-09-2.0, B-20-2.0, Glass MMVF11, Stone MMVF21, Slag MMVF22, M-Stone 3, and R-Stone-Experimental. The short, thin fibers included the following: Glass fibers B-09-0.6, B-20-0.6 [reported incorrectly in the Table 1 of Roller *et al.* (1997) as B-0.9-0.6, but the doses matched the B-20-0.6 fiber type], Glass fibers M-753-105, and the asbestoses crocidolite and tremolite. The probit model was fitted to the data, and each data set was constrained to a common slope (Figure 5-3).

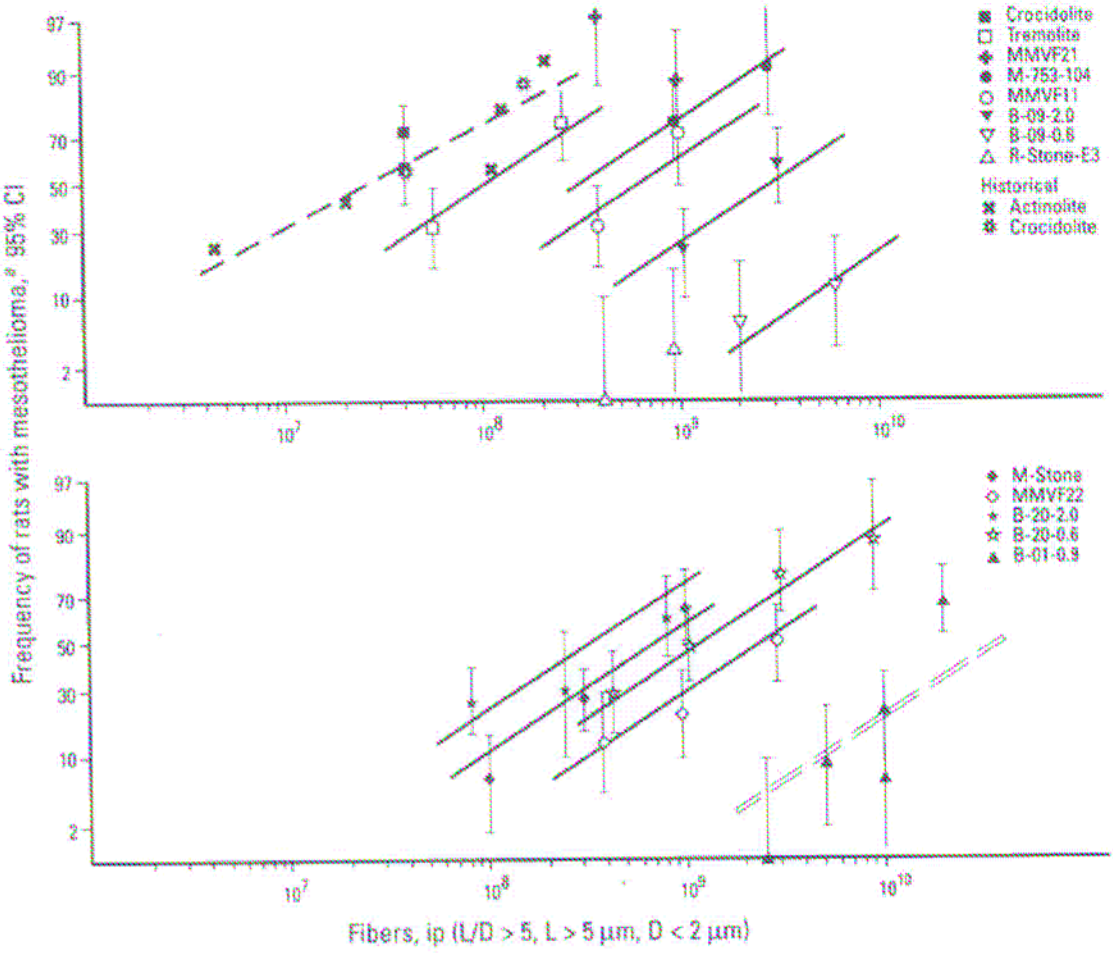

Figure 5-3. Probit analysis of the number of fibers injected (i.p.) and the frequency of peritoneal mesothelioma in rats

Combined data from three experiments (1990–1992). Combined results of asbestos studies (acrinolite and cricidolite; combined historical data) are presented in the top panel, broken line. Data are presented in 2 panels for clarity.

[a] Historical data for mesothelioma/sarcoma. L = length, D = Diameter
Source**:** Roller *et al.* 1997

(Data from crocidolite, R-Stone-Experimental 3, and MMVF21 were not included in the probit analysis because of results at the extremes of no response for R-Stone-Experimental 3 and near maximal response at the lowest dose tested for MMVF21 and crocidolite.) The normalized data for the various dusts were also plotted with a linear scale for frequency of mesothelioma, which resulted in a slightly superlinear curve (Figure 5-4). The authors fitted a curve separately to the data for the B-01-0.9 data, which resulted in a sublinear shape. The authors noted that this dust has a relatively low durability and was tested with the highest dose of 1,000 mg.

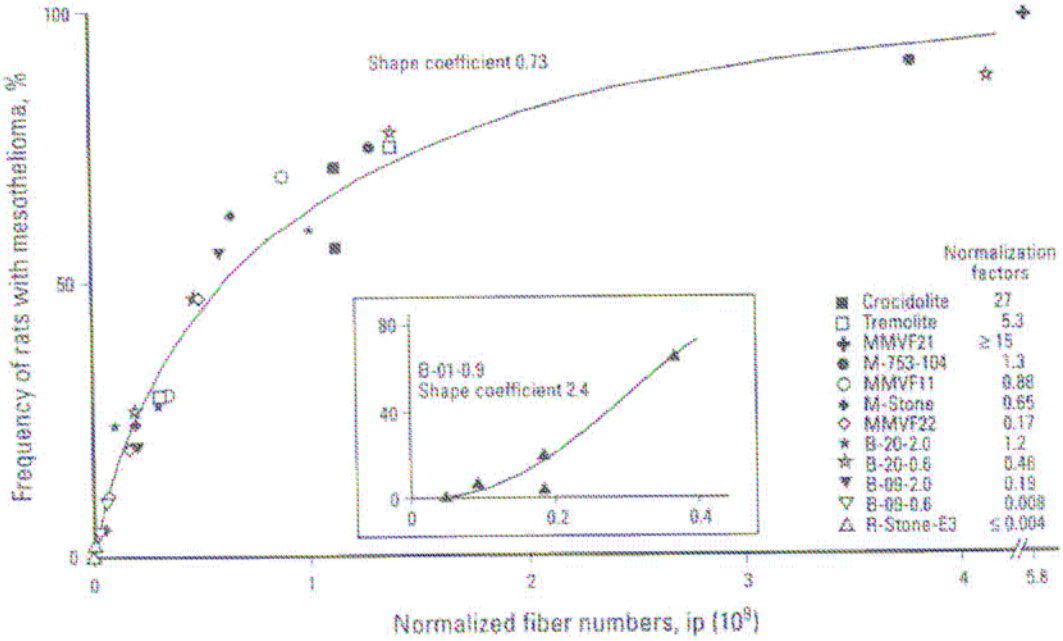

Figure 5-4. Percent incidence of mesothelioma after i.p. injection of various fiber dusts

Shape coefficient is calculated from the Weibull model and fitted to normalized data. Insert is for B 01-0.9 fiber (sublinear curve; dose values normalized so that scale of the x-axis is comparable to the larger plot).

Source**:** Roller *et al.* 1997

The overall conclusion by Roller *et al.* (1997) was that the mechanism responsible for mesotheliomas in their experimental system was specific to the fibrous shape of the particles administered based on parallelism of the probit lines calculated for each fiber type.

Lambre *et al.* (1998) compared the carcinogenic potential of 5 MMVFs, 2 glass wools (A and C) and 3 stone wools (F, G, and H) (Table 5-1G). The samples had been specially manufactured and processed to produce fibers in the size range with median diameter less than 1 μm and median length between 10 and 15 μm. The stone wool fibers designated H had the highest weighted half-time (13 days) for persistence for fibers > 20 μm, although only slightly higher than the range of the other 4 fibers, which was 3.5 to 8.5 days. The H fibers caused 7/51 (14%) mesotheliomas at the highest dose (55 mg) tested, while none of the other fibers caused more than 2/51 (4%) tumors at any dose tested. The positive control, crocidolite, caused 20/51 (39%) tumors at the highest dose of 0.5 mg. The authors summarized the findings as showing that fibers with a high dissolution rate *in vitro* at pH 7.4 along with low biopersistence for fibers with length > 20 μm tended to have a low carcinogenic potency in the i.p. assay.

Miller *et al.* (1999) modeled the relationship between mesothelioma mortality and fiber characteristics. The results that the models were based on are reported in Table 5-1H. One model predicted decreasing survival with increasing numbers of longer fibers and increasing biopersistence. However, another model predicted increasing survival with increasing fiber numbers over 10 μm in length. The authors noted that they preferred the first model on the basis of plausibility. The fiber types tested were 100/475 glass microfibers, amosite, MMVF10 glass wool, MMVF21 and MMVF22 stone wool, and RCF1, RCF2, and RCF3 refractory ceramic fibers. [No control group was included.]

Grimm *et al.* (2002) tested 3 newly developed biosoluble insulation glass wool fibers (M, P, and V) and 1 newly developed biosoluble insulation stone wool fiber along with a previously developed biosoluble glass fiber (B) (Table 5-1I). Although fibers B (17%), P (15%), and V (27%) significantly increased tumor levels [statistical test and level of significance not reported], the authors reported that all of the fibers met the EC criteria for exoneration from carcinogenicity classification. Also, they noted that no statistical difference was found between fiber B and any of the other fibers, and that fiber B was named in the German TRGS 905 as a fiber that is not considered to have carcinogenic potential. The authors speculated that the German criterion based on a dose of 5×10^9 WHO fibers might not be valid for highly soluble mineral fibers.

Table 5-1A. Fibrous materials tested by Stanton *et al.* (1981)

Expt. No.	Compound	Actual tumor incidence	Percent tumor probability ± SD	Common log fibers/μg, ≤ 0.25 μm x > 8 μm	Expt. No.	Compound	Actual tumor incidence	Percent tumor probability ± SD	Common log fibers/mg, ≤ 0.25 mm x > 8 mm
1	Titanate 1	21/29	95 ± 4.7	4.94	37	Halloy 1	4/25	20 ± 9.0	0
2	Titanate 2	20/29	100	4.70	38	Halloy 2	5/28	23 ± 9.3	0
3	Si carbide	17/26	100	5.15	39	**Glass 8**	**3/26**	**19 ± 10.3**	**3.01**
4	Dawson 5	26/29	100	4.94	40	Crocid 11	4/29	19 ± 8.5	0
5	Tremolite 1	22/28	100	3.14	41	**Glass 19**	**2/28**	**15 ± 9.0**	**0**
6	Temolite 2	21/28	100	2.84	42	**Glass 9**	**2/28**	**14 ± 9.4**	**1.84**
7	Dawson 1	20/25	95 ± 4.8	4.66	43	Alumin 6	2/28	13 ± 8.8	0.82
8	Crocid 1	18/27	94 ± 6.0	5.21	44	Dawson 6	3/30	13 ± 6.9	0
9	Crocid 2	17/24	93 ± 6.5	4.30	45	Dawson 2	2/27	12 ± 7.9	0
10	Crocid 3	15/23	93 ± 6.9	5.01	46	Wollaston 2	2/25	12 ± 8.0	0
11	Amosite	14/25	93 ± 7.1	3.53	47	Crocid 12	2/27	10 ± 7.0	3.73
12	Crocid 4	15/24	86 ± 9.0	5.13	48	Attapul 2	2/29	11 ± 7.5	0
13	**Glass 1**	**9/17**	**85 ± 13.2**	**5.16**	49	**Glass 10**	**2/27**	**8 ± 5.6**	**0**
14	Crocid 5	14/29	78 ± 10.8	3.29	50	**Glass 11**	**1/27**	**8 ± 5.5**	**0**
15	**Glass 2**	**12/31**	**77 ± 16.6**	**4.29**	51	Titanate 3	1/28	8 ± 8.0	0
16	**Glass 3**	**20/29**	**74 ± 8.5**	**3.59**	52	Attapul 1	2/29	8 ± 5.3	0
17	**Glass 4**	**18/29**	**71 ± 9.1**	**4.02**	53	Talc 1	1/26	7 ± 6.9	0
18	Alumin 1	15/24	70 ± 10.2	3.63	54	**Glass 12**	**1/25**	**7 ± 5.4**	**0**
19	**Glass 5**	**16/25**	**69 ± 9.6**	**3.0**	55	**Glass 13**	**1/27**	**6 ± 5.7**	**0**
20	Dawson 7	16/30	68 ± 9.8	4.71	56	**Glass 14**	**1/25**	**6 ± 5.5**	**0**

Expt. No.	Compound	Actual tumor incidence	Percent tumor probability ± SD	Common log fibers/μg, ≤ 0.25 μm x > 8 μm	Expt. No.	Compound	Actual tumor incidence	Percent tumor probability ± SD	Common log fibers/mg, ≤ 0.25 mm x > 8 mm
21	Dawson 4	11/26	66 ± 12.2	4.01	57	**Glass 15**	**1/24**	**6 ± 5.9**	**1.30**
22	Dawson 3	9/24	66 ± 13.4	5.73	58	Alumin 7	1/25	5 ±5.1	0
23	**Glass 6**	**7/22**	**64 ± 17.7**	**4.01**	59	**Glass 16**	**1/29**	**5 ± 4.4**	**0**
24	Crocid 6	9/27	63 ± 13.9	4.60	60	Talc 3	1/29	4 ± 4.3	0
25	Crocid 7	11/26	56 ± 11.7	2.65	61	Talc 2	1/30	4 ± 3.8	0
26	Crocid 8	8/25	53 ± 12.9	0	62	Talc 4	1/28	5 ± 4.9	0
27	Alumin 2	8/27	44 ± 11.7	2.95	63	Alumin 8	1/28	3 ± 3.4	0
28	Alumin 3	9/27	41 ± 10.5	2.47	64	Glass 21	2/47	6 ± 4.4	0
29	Crocid 9	8/27	33 ± 9.8	4.25	65	Glass 22	1/45	2 ± 2.3	0
30	Wollaston 1	5/20	31 ± 12.5	0	66	Glass 17	0/28	0	0
31	Alumin 4	4/25	28 ± 12.0	2.60	67	Glass 18	0/115	0	0
32	Crocid 10	6/29	37 ± 13.5	3.09	68	Crocid 13	0/29	0	0
33	Alumin 5	4/22	22 ± 9.8	3.73	69	Wollaston 4	0/24	0	0
34	Glass 20	4/25	22 ± 10.0	0	70	Talc 5	0/30	0	0
35	Glass 7	5/28	21 ± 8.7	2.50	71	Talc 6	0/30	0	3.30
36	Wollaston 3	3/21	19 ± 10.5	0	72	Talc 7	0/29	0	0

Table 5-1B. Fibers tested by Pott *et al.* (1974)

Study design)	Fiber Type	K_{diss}, SiO_2 (ng/cm^2-h)	Z-score	Diameter	Length	Dose, mg	No. WHO fibers x 10^6	Tumor Incidence (mesothelioma)	Comments
Wistar rats (sex not reported) i.p. injection ?? wk of observation	Chrysotile A	NA	NA	NR	93.9% < 5µm	6 25 4 x 25	NR	27/40 (68) 26/40 (65) 15/40 (38)	
	Chrysotile A, milled	NA	NA	NR	99.8% < 5µm	4 x 25	NR	12/40 (30)	
	Glass fibers	NA	NA	0.5 (average)	72.6% < 5µm	4 x 25	NR	23/40 (58)	
	Gypsum	NA	NA	NR	75.0% < 5µm	4 x 25	NR	2/40 (5)	
	Nemalite	NA	NA	NR	96.4% < 5µm	4 x 25	NR	25/40 (62)	
	Palygorscite	NA	NA	NR	70.0% < 5µm	3 x 25	NR	26/40 (65)	
	Saline	–	–	–	–	4 x 2 mL	–	0/80 (0)	

Table 5-1C. Fibers tested by Pott *et al.* (1987)

Study design	Fiber Type	$T_{1/2}$, days (95% CI) *in vivo*	Z-score	Diameter (median)	Length (median)	Dose, mg	No. fibers x 10^9	Tumor incidence (sarcoma, mesothelioma, or carcinoma)	Comments
Wistar or Sprague-Dawley rats, 4–15 weeks old at beginning of experiment	**Experiment # 1**								Wistar rats, 12 weeks old at beginning of experiment
	Chrysotile, UICC/A	NA	NA	0.15	9	6	NR	27/34 (77)	
	Chrysotile, UICC/A	NA	NA	0.15	8	25	NR	25/31 (81)	
	Chrysotile, HCl treated	NA	NA	–	–	6	NR	0/38 (0)	
	Chrysotile, HCl treated	NA	NA	–	–	25	NR	–/40 (–)	
	Saline	–	–	–	–	–	–	0/70 (0)	
	Experiment # 2								Wistar rats, 12 weeks old at beginning of experiment
	Glass filaments, ES 5	NA	NA	5.5	39	10	NR	2/50 (4.0)	
	Glass filaments, ES 5	NA	NA	5.5	39	40 (2 x20)	NR	5/46 (11)	
	Glass filaments, ES 7	NA	NA	7.4	46	40 (2 x 20)	NR	1/47 (2)	
	Experiment # 3								Wistar rats, 15 weeks old at beginning of experiment
	Slag wool, RH	NA	NA	2.6	26	40 (2 x 20)	NR	6/99 (6)	
	Slag wool, Z1	NA	NA	1.5	14	40 (2 x 20)	NR	2/96 (2)	
	Saline	–	–	0.06	1.3	2 x 2 mL	–	48 (0)	
	Experiment # 4								Wistar rats, 12 weeks

Study design	Fiber Type	$T_{1/2}$, days (95% CI) *in vivo*	Z-score	Diameter (median)	Length (median)	Dose, mg	No. fibers x 10^9	Tumor incidence (sarcoma, mesothelioma, or carcinoma)	Comments
	Glass filaments, ES 5	NA	NA	5.5	39	250 (lap.)	NR	2/28 (7)	old at beginning of experiment lap. = laparotomia under nembutal anesthesia for inoculation in 4 mL saline
	Experiment # 5								NA
	Glass filaments, ES 3	NA	NA	3.7	16.5	50 (lap.)	NR	3/48 (6)	
	Glass filaments, ES 3	NA	NA	3.7	16.5	250 (lap.)	NR	4/46 (9)	
	Saline	–	–	–	–	4 mL (lap.)	–	2/45 (4)	
	Experiment # 6								Wistar rats, 12 weeks old at beginning of experiment
	Anthophyllite, UICC	NA	NA	0.61	2.6	2	NR	4/37 (11)	
	Anthophyllite, UICC	NA	NA	0.61	2.6	10	NR	17/39 (44)	
	Chrysotile, UICC/A milled	NA	NA	0.02	0.2	10	NR	1/39 (3)	
	Glass fibers, 106	NA	NA	0.47	2.2	10	NR	2/39 (5)	
	Nemalite	NA	NA	0.06	1.3	2	NR	28/37 (76)	
	Nemalite	NA	NA	0.06	1.3	10	NR	32/40 (80)	
	Experiment # 7								Wistar rats, 12 weeks old at beginning of experiment Females (f) and males (m) tested
	Glass fibers, 104/1974, Ch. 2	NA	NA	0.3	3.5	10	NR	13/26 (50) (f)	
	Glass fibers, 104/1974, Ch. 2	NA	NA	0.3	3.5	10	NR	18/33 (55) (m)	
	Experiment # 8								

Study design	Fiber Type	$T_{1/2}$, days (95% CI) *in vivo*	Z-score	Diameter (median)	Length (median)	Dose, mg	No. fibers x 10^9	Tumor incidence (sarcoma, mesothelioma, or carcinoma)	Comments
	Chrysotile, UICC/B milled	NA	NA	0.06	0.56	50	NR	1/41 (2)	Wistar rats, 12 weeks old at beginning of experiment
	Actinoline, F.R.G	NA	NA	0.17	1.9	2.5	NR	30.45 (67)	
	Experiment # 9								Wistar rats, 9 weeks old at beginning of experiment
	Attapulgite, Mormoiron	NA	NA	0.07	0.7	60 (5 inj.)	NR	4/114 (4)	
	Attapulgite, Lebrija	NA	NA	0.07	0.5	60 (5 inj.)	NR	4/115 (3)	
	Attapulgite, Georgia	NA	NA	0.04	0.8	60 (5 inj.)	NR	4/122 (4)	
	γ–ferric oxide hydrate (1)	NA	NA	0.07	0.5	135 (5 inj.)	NR	21/111 (19)	
	Experiment # 10								Sprague-Dawley rats, 10 weeks old at beginning of experiment
	Glass fibers, 104/1974, Ch. 1	NA	NA	4.8	0.29	5	NR	44/54 (82)	
	Glass fibers, HCl-treated, 2 h	NA	NA	–	–	5	NR	32/54 (59)	
	Glass fibers, HCl-treated, 24 h	NA	NA	5.3	0.5	5	NR	4/54 (7)	
	Glass fibers, NaOH-treated, 2 h	NA	NA	–	–	5	NR	42/54 (78)	
	Glass fibers, NaOH-treated, 24 h	NA	NA	5.4	0.5	5	NR	46/53 (87)	
	Erionite, Turkey	NA	NA	2.9	0.38	1.25	NR	38/53 (72)	
	Erionite, Turkey	NA	NA	2.9	0.38	5	NR	43/53 (81)	
	Erionite, Turkey	NA	NA	2.9	0.38	20	NR	37/53 (70)	
	Experiment # 11								

Study design	Fiber Type	$T_{1/2}$, days (95% CI) *in vivo*	Z-score	Diameter (median)	Length (median)	Dose, mg	No. fibers x 10^9	Tumor incidence (sarcoma, mesothelioma, or carcinoma)	Comments
	Glass fibers, 104/1974, Ch. 1	NA	NA	0.29	4.8	5	NR	20/45 (44)	Wistar rats, 4 weeks old at beginning of experiment
	Glass fibers, HCl-treated 24 h	NA	NA	0.5	5.3	5	NR	2/45 (4)	
	Glass fibers NaOH-treated 24 h	NA	NA	0.5	5.4	5	NR	27/46 (59)	
	Erionite, Turkey	NA	NA	0.38	2.9	5	NR	34/48 (71)	
	Actinolite, F.R.G.	NA	NA	0.17	1.9	0.5	NR	54/59 (92)	
	Experiment # 12								Sprague-Dawley rats, 8 weeks old at beginning of experiment
	Glass fibers, 100/Pen	NA	NA	0.33	2.4	2	NR	21/54 (39)	
	Glass fibers, 100/Pen	NA	NA	0.33	2.4	10	NR	24/53 (45)	
	Glass fibers, 100/L&V	NA	NA	0.32	4.4	2	NR	26/54 (48)	
	Rock wool, Sweden	NA	NA	1.9	23.0	75 (3 x 25)	NR	45/63 (71)	
	Rock wool, Sweden, fine	NA	NA	0.64	4.1	10	NR	6/45 (13)	
	NaCl-sol.	–	–	–	–	2 x 2 mL	–	–	
	Experiment # 13								Wistar rats, 5 weeks old at beginning of experiment
	Attapulgite, Caceres	NA	NA	0.07	1.3	10 (2 + 4 + 4)	NR	12/20 (40)	
	Erionite, Oregon	NA	NA	0.21	1.8	0.5	NR	15/31 (48)	
	Erionite, Oregon	NA	NA	0.21	1.8	2.0	NR	28/31 (90)	
	Actinolite, F.R.G.	NA	NA	0.17	1.9	0.3	NR	23/29 (79)	

Study design	Fiber Type	$T_{1/2}$, days (95% CI) *in vivo*	Z-score	Diameter (median)	Length (median)	Dose, mg	No. fibers x 10^9	Tumor incidence (sarcoma, mesothelioma, or carcinoma)	Comments
	Actinolite, PVNO separately	NA	NA	0.17	1.9	0.3	NR	21/32 (66)	
	Actinolite, in 1 mL 2% PVNO + PVNO separately	NA	NA	0.17	1.9	0.3	NR	14/29 (48)	
	Chrysotile, UICC/B	NA	NA	0.11	0.9	1.0	NR	27/32 (84)	
	Chrysotile, PVNO separately	NA	NA	0.11	0.9	1.0	NR	24/30 (80)	
	Chrysotile, Calidria	NA	NA	0.03	1.2	0.5	NR	2/32 (6)	
	Crocidolite, South Africa	NA	NA	0.20	2.1	0.5	NR	18/32 (56)	
	Crocidolite, South Africa	NA	NA	0.20	2.1	2.0	NR	28/32 (88)	
	Glass fibers, 104/475	NA	NA	0.18	3.2	0.5	NR	5/30 (17)	
	Glass fibers, 104/475	NA	NA	0.18	3.2	2.0	NR	8/31 (26)	
	Glass fibers, HCl-treated 24 h	NA	NA	–	–	2.0	NR	16/32 (50)	
	Kevlar fibers (1)	NA	NA	–	–	10 (2 + 4 + 4)	NR	4/31 (13)	
	Saline	–	–	–	–	1 x 1 mL	–	2/32 (6)	
	Experiment # 15								Wistar rats, 8 weeks old at beginning of experiment Preliminary results 28 mo after i.p. injections
	Actinolite, F.R.G.	NA	NA	0.17	1.9	0.01	NR	3/35 (9)	
	Actinolite, F.R.G.	NA	NA	1.17	1.9	0.05	NR	11/36 (31)	
	Actinolite, F.R.G.	NA	NA	0.17	1.9	0.25	NR	20/36 (56)	

Study design	Fiber Type	$T_{1/2}$, days (95% CI) *in vivo*	Z-score	Diameter (median)	Length (median)	Dose, mg	No. fibers x 10^9	Tumor incidence (sarcoma, mesothelioma, or carcinoma)	Comments
	Actinolite, in 1 mL 0.4% PVNO	NA	NA	0.17	1.9	0.25	NR	9/35 (26)	mo after i.p. injections Total # rats = Rats examined + survivors at 28 mo
	Actinolite, in 1 mL 2% PVNO	NA	NA	0.17	1.9	0.25	NR	9/36 (25)	
	Chrysotile, UICC/B	NA	NA	0.11	0.9	0.05	NR	7/36 (20)	
	Chrysotile, UICC/B	NA	NA	0.11	0.9	0.25	NR	21/34 (62)	
	Chrysotile, UICC/B	NA	NA	0.11	0.9	1.00	NR	31/36 (86)	
	Glass fibers, 104/475	NA	NA	0.18	3.2	5 (5 x 1)	NR	35/53 (66)	
	Basalt wool, G + H	NA	NA	1.8	20.0	75 (5 x 15)	NR	32/53 (60)	
	Ceramic wool, Fiberfrax	NA	NA	0.91	8.3	45 (5 x 9)	NR	32/47 (68)	
	Ceramic wool, MAN	NA	NA	1.1	6.9	75 (5 x 15)	NR	12/54 (22)	
	Wollastonite	NA	NA	1.1	5.2	100 (5 x 20)	NR	0/54 (0)	
	γ-Ferric oxide hydrate (2)	NA	NA	0.03	0.5	250 (5 x 50)	NR	6/49 (12)	
	α-Ferric oxide hydrate	NA	NA	0.01	0.1	20 (5 x 4)	NR	1/51 (2)	
	Kevlar fibers (2)	NA	NA	0.47	3.9	50 (5 x 10)	NR	3/52 (6)	
	Polypropylene fibers	NA	NA	1.1	7.4	500 (5 x 100)	NR	1/51 (2)	
	NaCl-sol.	–	–	–	–	5 x 2 mL	–	2/102 (2)	

Table 5-1D. Fibers tested by Pott *et al.* (1989)

Study design	Fiber Type	K_{diss}, SiO_2 (ng/cm^2-h)	Z-score	Diam.	Length	Dose, mg	No. fibers x 10^6	Tumor Incidence (mesothelioma)	Comments
Female Wistar rats, 8 weeks old at start i.p. injection 130 wk of observation	Actinolite, F.R.G.	NA	NA	0.10	1.10	0.01 0.05 0.25 0.25 (0.4% PVNO) 0.25 (2% PVNO)	102[a]	8/35 (23) 15/36 (42) 20/36 (56) 8/35 (23 12/36 (33)	
	Chrysotile, Canadian, UICC	NA	NA	0.05	0.67	0.05 0.25 1.00	202 [a]	12/36 (33) 23/34 (68) 30/36 (83)	
	Glass fibers, 104/475	NA	NA	0.15	2.6	5 (5 x 1)	680	34/53 (64)	
	Basalt wool	NA	NA	1.1	17	75 (5 x 15)	59	30/53 (57)	
	Ceramic wool, Fiberfrax	NA	NA	0.89	13	45 (5 x 9)	150	33/47 (70)	
	Ceramic wool, Manville	NA	NA	1.4	16	75 (5 x 15)	21	0/54 (0)	
	Wollastonite, India	NA	NA	1.1	8.1	100 (5 x 20)	430	0/80 (0)	
	γ-Ferric oxide	NA	NA	~0.03	~0.5	250 (5 x 50)	NR	8/49 (16)	
	α-Ferric oxide	NA	NA	~0.01	~0.1	250 (5 x 50)	NR	2/51 (4)	
	Kevlar fibers	NA	NA	0.48	4.9	20 (5 x 4)	1260	3/53 (6)	
	Sodium chloride solution	–	–	–	–	10 mL (5 x 2 mL)	–	2/102 (2)	

[a]Only a single value was reported for fiber number, and the authors did not relate that number to the dose in mg.

Table 5-1E. Fibers tested by Pott *et al.* (1991)

Study design	Fiber Type	$T_{1/2}$, days (95% CI) *in vivo*	Z-score	Diameter (median)	Length (median)	Dose, mg	No. fibers x 10^9	Tumor Incidence (mesothelioma)	Comments
Results from Table 2	Saline	NA	NA	NA	NA	0	0	2/50 (4)	Biopersistence reported by (Muhle *et al.* 1991) K = short M = medium L = long
	B-1 (glass wool)	107 (98–119)	35.8	1.06 1.06 1.68 1.68 1.19 1.40 1.40	K – 7.4 K – 7.4 M – 10.7 M – 10.7 ML – 11.0 L – 17.8 L – 17.8	3 x 20 3 x 50 1 x 20 3 x 20 2 x 50 1 x 20 3 x 20	0.24 0.60 0.05 0.16 0.51 0.04 0.11	3/46 (7) 1/32 (3) 1/48 (2) 1/46 (2) 1/39 (2) 1/48 (2) 5/46 (11)	
	B-2 (glass wool)	38 (35–41)	35.8	0.49 0.49 0.51 0.51 0.51	K – 4.2 K – 4.2 L – 6.0 L – 6.0 L – 6.0	1 x 6.7 1 x 20 1 x 6.7 1 x 20 2 x 50	0.29 0.86 0.39 1.16 5.8	0/48 (0) 0/46 (0) 0/45 (0) 2/44 (5) 1/35 (3)	
	B-3 (glass wool)	238 (183–340)	15.7	0.37 0.37 0.34 0.34	K – 3.3 K – 3.3 L – 5.6 L – 5.6	1 x 6.7 1 x 20 1 x 6.7 1 x 20	0.38 1.14 0.15 0.46	10/48 (21) 30/47 (64) 19/48 (40) 31/47 (66)	
	JM475	NR	21.0	0.40	10.60	1 x 2	0.32	8/48 (17)	
Results from Table 3	B-1 (glass wool)	107 (98–119)	35.8	1.06 1.19	K – 7.4 ML – 11.0	3 x 50 2 x 50	0.60 0.51	1/32 (3.1) 1/39 (2.6)	
	B-2 (glass wool)	38 (35–41)	35.8	0.51	L – 6.0	2 x 50	5.80	1/35 (2.9)	
	Ca-Na-metaphosphate	NA	NA	0.30 0.30	2.8 2.8	1 x 50 5 x 50	0.26 1.29	3/17 (17.6) 4/16 (25.0)	
	Gypsum A 30	NA	NA	1.34	11.2	5 x 50	0.19	1/24 (4.2)	

Study design	Fiber Type	$T_{1/2}$, days (95% CI) *in vivo*	Z-score	Diameter (median)	Length (median)	Dose, mg	No. fibers x 10^9	Tumor Incidence (mesothelioma)	Comments
	Gypsum H 30	NA	NA	0.98	9.7	5 x 50	0.16	0/12 (0)	
	Mg-oxide-sulphate	NA	NA	0.19 0.19	2.2 2.2	1 x 50 10 x 15	5.98 17.9	1/21 (4.8) 0/10 (0)	
	Sepiolite, Uicaluaro	NA	NA	0.06 0.06	1.0 1.0	1 x 50 5 x 50	7.56 37.8	0/23 (0) 2/21 (9.5)	
	Basalt	NA	NA	1.08 1.08	13.8 13.8	1 x 25 5 x 30	0.005 0.030	1/38 (2.6) 15/21 (71.4)	
	Slag	NA	NA	1.21	9.0	5 x 30	0.25	2/28 (7.1)	
	Silicon carbide	NA	NA	0.31 0.31 0.31 0.31 0.31	3.1 3.1 3.1 3.1 3.1	1 x 0.05 1 x 0.25 1 x 1.25 1 x 6.25 1 x 25	0.005 0.27 0.13 0.67 2.68	2/16 (12.5) 5/23 (21.7) 13/21 (61.9) 23/30 (76.7) 36/37 (97.3)	
	Carbon	NA	NA	17.7 17.7	193 193	1 x 50 5 x 50	0 0	0/25 (0) 0/20 (0)	
	NaCl solution	–	–	–	–	5 x 2 mL	–	2/50 (4)	
Results from Table 4	Al-silicate "Fiberfrax" I	NA	NA	0.47	5.5	1 x 12	0.029	15/35 (42.9)	
	Al-silicate "Fiberfrax" II	NA	NA	0.84 0.84	13.1 13.1	1 x 12 2 x 20	0.021 0.069	17/36 (47.2) 29/36 (80.6)	
	Al-silicate, Manville5	NA	NA	1.35	16.4	2 x 20	0.009	6/36 (16.7)	
	Potassium titanate	NA	NA	0.22 0.22	3.2 3.2	1 x 0.5 1 x 2	0.045 0.18	1/34 (2.9) 11/36 (30.6)	
	NaCl solution	–	–	–	–	50 x 1 mL	–	0/34 (0)	

Table 5-1F. Fibers tested by Roller *et al.* (1996, 1997)

Study design	Fiber Type	$T_{1/2}$, days (95% CI) *in vivo*	Z-score	Diameter (median)	Length (median)	Dose, mg (sex)	No. fibers x 10^9	Tumor Incidence (mesothelioma)	Comments
Male & female Wistar rats i.p. injection up to 30 mo of observation	Untreated	NA	NA	NA	NA	0 (F)	0	0/37 (0)	
	Saline	NA	NA	NA	NA	20 x 2 mL (F) 20 x 2 mL (M) 20 x 2 mL (F)	0	0/93 (0) 1/69 (1) 0/38 (0)	
	Crocidolite	NA	4.3-14.6	0.19	1.8	5 x 0.1 (F) 5 x 0.1 (M) 5 x 0.1 (F)	0.042 0.042 0.042	25/32 (78) 32/48 (67) 20/39 (51)	
	Tremolite	NA	32-411	0.29	3.4	1 x 3.3 (F) 1 x 15 (F)	0.057 0.26	9/40 (23) 30/40 (75)	
	M-753-104 (vitreous fibers)	NA	24.8	0.22	~3.3	1 x 17 (F) 1 x 50 (F)	1.0 2.9	30/40 (75) 36/40 (90)	
	MMVF-11 (vitreous fibers)	199 (172-235)	27.1	0.77	14.6	2 x 35 (F) 6 x 30 (F)	0.4 1.0	12/40 (30) 16/23 (70)	
	B-01-0.9 (vitreous fibers)	32 (26-45)	35.8	~0.7	9.60	5 x 25 (F) 10 x 25(F) 20 x 25 (F) 20 x 25 (M) 40 x 25 (M)	2.5 5.0 10.0 10. 20.0	3/39 (8) 4/37 (11) 3/36 (8) 10/48 (21) 33/50 (66)	
	B-09-0.6 (vitreous fibers)	NA	26.7	0.49	3.3	2 x 50 (F) 6 x 50 (F)	2.0 6.1	1/40 (3) 4/39 (10)	

Study design	Fiber Type	$T_{1/2}$, days (95% CI) *in vivo*	Z-score	Diameter (median)	Length (median)	Dose, mg (sex)	No. fibers x 10^9	Tumor Incidence (mesothelioma)	Comments
	B-09-2.0 (vitreous fibers)	NA	26.7	1.19	10.5	3 x 50 (F) 9 x 50 (F)	1.1 3.2	9/40 (23) 21/40 (53)	
	B-20-0.6	NA	38	0.30	3.6	1 x 3.5 (F) 1 x 8.5 (F) 1 x 25 (F) 3 x 25 (F)	0.4 1.0 3.0 9.0	12/40 (30) 17/40 (43) 30/40 (75) 27/32 (87)	
	B-20-2.0	NA	38	0.77	7.8	1 x 6 (F) 1 x 6 (M) 1 x 18 (F) 1 x 18 (M) 2 x 30 (M)	0.08 0.08 0.24 0.24 0.8	2/32 (6) 15/36 (42) 7/32 (22) 12/34 (35) 21/35 (60)	
	MMVF-21	326 (266-421)	30.2	1.02	16.9	2 x 30 (F) 5 x 30 (F)	0.4 1.0	37/38 (97) 33/38 (87)	
	R-stone-E3	32 (29-36)	47.3	1.03	16.9	4 x 28.5 (F) 9 x 28.5 (F)	0.4 0.9	0/38 (0) 4/35 (11)	
	M-stone	116 (108-126)	37.1	0.84	10.1	1 x 8.5 (F) 1 x 8.5 (M) 1 x 25.5 (F) 1 x 25.5 (M) 2 x 42.5 (M)	0.1 0.1 0.3 0.3 1.0	2/32 (6) 2/36 (6) 9/32 (28) 8/36 (22) 22/35 (63)	
	MMVF-22	81 (75-89)	48.2	0.77	8.7	1 x 20 (F) 1 x 50 (F) 3 x 50 (F)	0.4 1.0 2.9	4/40 (10) 8/40 (20) 18/38 (47)	

Table 5-1G. Fibers tested by Lambre *et al.* (1998)

Study design	Fiber Type	K_{diss}, SiO_2 (ng/cm^2-h)	Z-score	Diameter (mean)	Length (mean)	Dose, mg	No. fibers x 10^6	Tumor Incidence (mesothelioma)	Comments
Female Wistar rats i.p. injection 130 wk of observation	Saline	NA	NA	NA	NA	NA	0 0	0/51 (0) 0/51 (0)	The authors reported a marked increase in mesotheliomas in groups treated with crocidolite at 0.05 and 0.5 mg and Fiber H at 55 mg
	Crocidolite	< 1	9.81	0.29	9.4	0.005 0.050 0.500	1.9 18.9 188.6	4/51 (8) 8/51 (16) 20/51 (39)	
	Fiber A (glass wool)	129	26.7	0.70	24.6	0.7 2.1 7.0 17.5 x 2	11.1 32.7 111.3 556.5	2/51 (4) 0/51 (0) 0/51 (0) 1/51 (2)	
	Fiber C (glass wool)	309	26.74	0.69	27.2	0.7 2.1 7.0 17.5 x 2	15.4 46.3 153.7 768.3	1/51 (2 1/51 (2) 0/51 (0) 0/51 (0)	
	Fiber F (stone wool)	96	36.35	0.72	15.8	1.1 7.7 55.0	13.9 97.1 693.3	2/51 (4) 0/51 (0) 1/51 (2)	
	Fiber G (stone wool)	129	32.75	0.74	16.0	1.1 7.7 55.0	11.6 81.5 582.3	1/51 (2) 0/51 (0) 1/51 (2)	
	Fiber H (stone wool)	139	35.27	0.79	17.1	1.1 7.7 55.0	6.7 46.9 334.8	1/51 (2) 0/51 (0) 7/51 (14)	

Table 5-1H. Fibers tested by Miller *et al.* (1999b)

Study design	Fiber Type	K_{diss}, SiO_2 (ng/cm^2-h)	Z-score	Diameter (median) μm	Length μm	Dose, mg	No. fibers x 10^9 < 0.95; > 0.95	Tumor Incidence (mesothelioma)	Comments
Male Wistar rats i.p. injection	100/475 (glass microfiber)	9.1	16	> 0.95 < 0.95	> 5	8.3	1.868; 0.012	8/24 (33)	Inject doses selected to provide an estimated 10^9 fibers > 5 μm in length. Fiber numbers reported separately for < 0.95 μm and > 0.95 μm diameter
	Amosite	0.2	1.8	> 0.95 < 0.95	> 5	6.1	0.402; 0.008	21/24 (92)	
	MMVF10 (glass wool)	122.4	NA	> 0.95 < 0.95	> 5	144.4	0.314; 0.659	13/22 (59)	
	MMVF21 (stone wool)	28.9	NA	> 0.95 < 0.95	> 5	183.1	1.012; 0.644	19/20 (95)	
	MMVF22 (stone wool)	52.8	NA	> 0.95 < 0.95	> 5	129.6	0.671; 0.544	13/24 (54)	
	RCF 1 (refractory ceramic fiber)	4.4	NA	> 0.95 < 0.95	> 5	110.9	0.394; 0.374	21/24 (88)	
	RCF 2 (refractory ceramic fiber)	3.1	NA	> 0.95 < 0.95	> 5	188.8	0.619; 0.550	13/18 (72)	
	RCF 4 (refractory ceramic fiber)	0.5	NA	> 0.95 < 0.95	> 5	90.4	0.264; 0.466	0/22 (0)	

Table 5-1I. Fibers tested by Grimm *et al.* (2002)

Study design	Fiber Type	K_{diss}, SiO_2 (ng/cm^2-h)	Z-score	Diameter (median)	Length (median)	Dose, mg	No. WHO fibers x 10^6	Tumor Incidence (mesothelioma)	Comments
Female Wistar rats i.p. injection 123 wk of observation	Untreated	NA	NA	NA	NA	0	0	0/51 (0)	$T_{1/2}$ for WHO fibers: B fibers = 17 d M fibers = 8.5 d O fibers = 8.5 d P fibers = 21.0 d V fibers = not det.
	Saline	NA	NA	NA	NA	20 x 2.5 mL	0	0/51 (0)	
	Crocidolite	~1	9.81	0.30	6.90	0.5 5.0	100 1000	27/51 (53) 45/51 (88)	
	B (glass wool)	580	34.42	0.52	8.90	216.4 541.0	2000 5000	3/51 (6) 9/53 (17)	
	M (glass wool)	103.7	30.04	0.41	7.70	41.0 164.0 410.0	500 2000 5000	0/50 (0) 0/51 (0) 0/52 (0)	
	O (stone wool)	523	26.67	0.40	10.60	53.65 214.6 536.5	500 2000 5000	0/51 (0) 1/51 (2) 0/51 (0)	
	P (glass wool)	610	45.45	0.40	9.60	51.15 204.6 511.5	500 2000 5000	0/51 (0) 4/51 (8) 8/52 (15)	
	V (glass wool)	450	26.36	0.80	9.90	72.4 289.6 724.0	500 2000 5000	2/51 (4) 1/51 (2) 14/51 (27)	

5.3.2 Summary of studies

The early studies with glass fibers and asbestos applied directly to the lung pleura (intrapleural implantation) of rats were interpreted by their authors as supporting the conclusion that long, thin glass fibers induced tumor formation as well as similarly sized asbestos (Stanton and Wrench 1972, Stanton *et al.* 1977, 1981). Based on induction of significant numbers of pleural sarcomas by fine, durable glass fibers and several other fiber types, including asbestos fibers, it was concluded that fiber dimensions and durability were important determinants of tumorigenicity. Following these early studies, most investigators have tested fibers by intraperitoneal injection. The authors of many of these studies concluded that there was a relationship between fiber dimensions and durability; however, [several studies have reported results that suggested that the relationship might not completely explain the data.]

In a study that examined the dose-response relationship for fiber types of different dimensions and *in vivo* durabilities, a series of probit lines for different fiber types was calculated, and the authors' overall conclusion was that the mechanism responsible for mesotheliomas in their experimental system was specific to the fibrous shape of the particles administered based on the parallel lines obtained (Roller *et al.* 1996, 1997). A similar conclusion resulted from regression modeling, which resulted in a model that predicted decreasing survival with increasing numbers of longer fibers and increasing biopersistence (Miller *et al.* 1999). A study that compared the rate of mesothelioma formation with *in vitro* fiber dissolution rate and biopersistence for fibers with length > 20 μm concluded that fibers with a high dissolution and low biopersistence for fibers tended to have a low potency in the i.p. assay (Lambre *et al.* 1998).

As noted above, some studies reported results that suggest that the relationship between fiber dimensions and durability might not completely explain the tumorigenicity of various fibers. One study that compared the tumorigenicity of glass fibers with asbestos and other natural fibers suggested that fibers less than 10 μm in length and with diameter less than 0.5 μm could still cause tumors by i.p. injection (Pott *et al.* 1974). In another study, pretreatment of fibers with HCl decreased the weight of glass fibers without

changing the physical dimensions of the fibers measurably or visibly corroding them, but tumorigenicity was decreased markedly (Pott *et al.* 1984a) (see Section 4.4). The authors of that study suggested that alterations in the rate of dissolution or disintegration of the fibers or their migration within tissues were possible explanations for their observations. Another set of observations that were not entirely consistent with the proposed role for fiber dimensions in determining tumorigenicity were reports of "unexpectedly strong" tumorigenic effects of relatively thick rock and ceramic fibers even though one study reported that the number of fibers injected per rat was smaller for these fiber types than for the glass fibers (Pott *et al.* 1987, 1989). In one of these studies (Pott *et al.* 1989), the authors also pointed out that actinolite and 104/475 glass fibers had similar size distributions based on the available data and that both fibers were durable in rats; however, the number of fibers that induced tumors at approximately a 60% rate was much greater for the glass fibers than for the actinolite fibers. In addition, the number of fibers longer than 5 μm was similar in 0.25 mg of actinolite and 75 mg of basalt fibers, and these preparations resulted in similar tumor incidences (56% for actinolite and 57% for basalt). An explanation put forward by the authors of the latter study was that either the percentage of very long (> 20 μm) fibers in the two preparations or some unknown surface properties might explain the unexpected results. A study of newly developed biosoluble insulation glass wool fibers (Grimm *et al.* 2002) reported statistically significant increases in tumor formation for a fiber type (B fibers) that had been reported in German regulations as exonerated from carcinogenicity classification, which the authors suggested might indicate that highly soluble mineral fibers did not fit within the German testing criteria.

[The concept that fiber dimensions and durability/biopersistence are related to the potential tumorigenicity of those fibers was developed using data from a broad range of fiber types as summarized here, and that concept continues to be generally accepted. The results summarized above that do not appear to fit neatly within that relationship are possibly due to the difficulty of applying the general principal to data sometimes obtained with a relatively narrow range of fiber characteristics under different experimental conditions.]

5.3.3 Inhalation studies

Hesterberg and Hart (2001) reviewed data from various inhalation studies in rats and compared lung deposition, biopersistence, and *in vitro* dissolution with pathogenicity of various fiber types. The authors reported that the results of these studies clearly indicated a relationship between biopersistence in the lung and pathogenicity (see Table 5-1). Characteristics of the more pathogenic fibers included little or no change in chemical composition, morphology, or fiber dimensions (which the authors interpreted as suggesting no significant dissolution or transverse fragmentation), and preferential clearance of shorter fibers. The nonpathogenic fibers showed chemical composition and surface changes, a decrease in average fiber dimensions, and a more rapid decrease in the number of long fibers compared with short fibers. Data from the biopersistence studies for amosite and crocidolite asbestos are compared with special-purpose fibers (MMVF32 and MMVF33) and glass wool (MMVF10 and MMVF11) in Table 5-1. This table shows much faster clearance half-times for insulation glass fibers MMVF10 and MMVF11 compared with the special-purpose glass fibers MMVF32 and MMVF33. In accord with this difference are the *in vitro* dissolution rates of the different fiber types.

Table 5-2. Comparison of the lung deposition, biopersistence, *in vitro* dissolution, and pathogenicity of glass wool and asbestos fibers

Fiber	Exposure (fibers/cm^3)		Lung deposition[a]			Clearance halftime, fibers > 20 μm (days)	In vitro dissolution[b]		Chronic inhalation pathogenicity	
	> 5 μm	> 20 μm	Total	> 5 μm	> 20 μm		pH 7.4	pH 4.5	Fibrosis	Tumors
Amosite	700	235	22.6	10.9 ± 1	1.6 ± 0.3	418	< 1	nd	+	+
Crocidolite	2,600	290	99.6	29.8 ± 7.1	1.0 ± 1.0	817	< 1	nd	+	+
MMVF32 E glass	400	150	7.6	5.7 ± 1.3	1.3 ± 0.3	79	9	7	+	+
MMVF33 475 glass	400	150	9.8	7.1 ± 0.6	1.4 ± 0.3	49	12	13	+	±
MMVF10 glass wool	250-350	100	13.8	8.6 ± 1.6	1.0 ± 0.2	14.5	300	329	–	–
MMVF11 glass wool	250-350	100	8.6	5.6 ± 1.2	1.0 ± 0.2	9	100	25	–	–

Source:Hesterberg and Hart 2001.

[a] Rats were exposed 6 hours/day for 5 days. Reported lung burdens were determined one day after exposure stopped.

[b] ng/cm^2/h

5.3.4 Modeling studies

In a review of the characteristics of various SVFs (including glass wool, stonewool, slagwool, and refractory ceramic fibers) and their influence on biopersistence and toxicity, Bernstein *et al*. (2001a) reported that biopersistence clearance half-time is a good predictor of both the pathological response (collagen deposition) observed in chronic inhalation studies and the tumor response observed in i.p. injection studies. In previous studies, Bernstein *et al.* (2001a, 2001b) investigated the relationship of fiber biopersistence with pathogenicity. Biopersistence clearance half-times (for fibers > 20 μm) from both inhalation and intratracheal instillation studies were used. Weighted half-times and slow clearance half-times were evaluated from inhalation biopersistence studies, while clearance half-times for various categories of fiber dimensions, including WHO fibers and fibers longer than 20 μm, were evaluated from intratracheal instillation biopersistence studies. One study examined the relationship of biopersistence with chronic inhalation toxicity in rats at 24 months (collagen deposition at the broncho-alveolar junction) while the other study used tumor response data from chronic i.p. studies in rats. Collagen deposition was selected because it is a precursor to fibrosis, which is associated with tumor response. Five SVFs (including MMVF10 and MMVF11) from 15 exposure groups were available from inhalation studies, while nine SVFs from 24 exposure groups were available from i.p. studies. Both weighted and slow-phase clearance times of long fibers from inhalation biopersistence studies were equally good predictors of lung fiber burdens and collagen score (Bernstein *et al.* 2001a). Clearance half-times of WHO fibers and long fibers from intratracheal instillation studies also were good predictors of collagen scores. The authors reported an apparent threshold for collagen formation of approximately 500,000 long fibers in the lung. Most of the animals examined (42 of 48) that had fewer fibers in the lung had a collagen score of 0.

Biopersistence half-times determined from inhalation or intratracheal instillation studies were equally good predictors of tumor response in chronic intraperitoneal injection studies (Bernstein *et al.* 2001b). The logistic regression analysis included median fiber length, number of fibers injected, and biopersistence half-times. The authors calculated R^2 (a measure of goodness of fit of the model) values for individual data and grouped

(mean) data. The range of values reported for R^2 (grouped) was 0.860 to 0.901 and for R^2 (individual) it was 0.471 to 0.494. Because the only difference between the models was whether intratracheal or inhalation measurements of WHO or L20 fibers were used and the R^2 values were very similar, the authors concluded that the models are equally as good in predicting intraperitoneal results. The data demonstrated that there was little difference in the various measures of biopersistence and that fiber length and number were important to the analysis. Therefore the authors concluded that comparisons of potency between different fiber types must be based on studies that use fibers of the same length and that, unlike inhalation studies, there was no apparent threshold for intraperitoneally injected fibers.

Berry (1999) developed a model for cumulative mesothelioma incidence as it related to fiber biopersistence in humans and rats. The predicted effect of biopersistence was investigated using a mesothelioma incidence model that included an exponential term representing elimination over time. The incidences generated by the model were then applied over the lifetime of reference groups with mortality from other causes. For humans, occupational exposure was taken as continuous from age 20 to 60 years or until death, if earlier, and the cumulative incidence of mesothelioma was calculated to 100 years for various elimination rates. For rats, exposure was a single injection [site of injection not stated] of fibers at 6 weeks of age and cumulative incidence of mesotheliomas was calculated up to 160 weeks post injection. The model was standardized for cumulative incidence of mesothelioma for a durable fiber (elimination constant, 0.01/year) at 50% for 75-year-old men and 110 weeks post-injection for rats. The author reported that the predicted carcinogenic effect in humans dropped off rapidly as the dissolution rate increased; whereas, the decrease only occurred with the least durable fibers in rats. The effect of fiber elimination rate on the mesothelioma rate was 17 times higher in humans than in rats. Berry concluded that relatively soluble fibers (*e.g.*, glass wool) that do not produce disease in rats are even less likely to produce disease in humans, most likely because rats age and develop cancer at a much quicker rate than humans. Therefore, the influence of fiber dissolution is less in rats. [In terms of a species life-time, a fiber that persists for 2 years is durable for the rat but not for humans.]

Rödelsperger (2004) further evaluated the extrapolation of the carcinogenic potency of fibers from rats to humans. Using the Berry model, he compared predicted mesothelioma incidences in humans (at 85 years of age) and rats (at 136 weeks of age) from graphs of percent mesothelioma vs. elimination constant for highly durable crocidolite fibers (elimination constant of 0.1/year) with less durable refractory ceramic fibers (elimination constant of 1.0/year). The predicted tumor incidence for crocidolite was about 4,750 times higher than for the less durable fiber in humans but only about 3.2 times higher in rats. Rödelsperger noted that the carcinogenic potency of refractory ceramic fibers and crocidolite were similar in rats when administered by inhalation or i.p. injection. He concluded that this similarity cannot be assumed for humans because of the greater effect of the dissolution rate in humans compared with rats. However, he noted it is unlikely that refractory ceramic fibers are as carcinogenic as crocidolite asbestos in humans.

5.4 Toxic effects

This section describes toxicity studies in humans and experimental animals.

5.4.1 Humans

Mortality from non-malignant diseases was also evaluated in some of the cohort and nested case-control mortality studies of glass fiber production workers discussed in the human cancer studies. (See Section 3.1 for a detailed description of the study population and methodology). In addition several other studies evaluated respiratory disease morbidity and are discussed below.

Respiratory effects: mortality studies

No significant increase in mortality from non-malignant respiratory disease (NMRD), excluding influenza and pneumonia was observed among the 32,110 fiberglass and mineral production workers followed until 1992 (SMR = 0.92, 95% CI = 0.84 to 1.02, 440 deaths compared with local rates) or 4,008 female workers (SMR = 1.02, 95% CI = 0.74 to 1.37, 44 deaths) in the 10-plant U.S. cohort established by Marsh and colleagues (Marsh *et al.* 2001a, Stone *et al.* 2004). Earlier publications of an overlapping cohort (16,661 male mineral wool and fiberglass workers at 17 plants, and followed until 1977, 1982, or 1985) found significant SMRs for NMRD (excluding influenza and pneumonia)

(SMRs =1.30, 129 deaths , $P < 0.01$ for the 1977 follow-up, and SMR = 1.32, 230 deaths, $P < 0.01$ for 1982, and SMR = 1.29, 281 deaths, $P < 0.01$ for 1985); however, no relationship was observed with cumulative exposure to respirable fibers (Enterline *et al.* 1983, Enterline *et al.* 1987, Marsh *et al.* 1990). Among workers employed at the 3 plants manufacturing fine fibers, higher SMRs were found for ever-exposed workers (at each plant) compared with non-exposed workers. In a case-control study of employees at the Owens-Corning Fiberglas plant in Newark, Ohio (one of the 10 plants in the Marsh cohort), a non-significant increased risk (OR = 1.50, 95% CI = 0.55 to 4.08) of NMRD was observed among workers with cumulative exposure of > 300 respirable fibers/cm^3 in conditional regression analyses (Chiazze *et al.* 1993) however, no increased risk in mortality was found in a smaller case-control study (30 cases and 103 matched controls) at another plant in Kansas City, Kansas (Chiazze *et al.* 2002).

Nonsignificantly increased SMRs for respiratory disease were reported in the Canadian cohort (SMR =1.19, 95% CI = 0.74 to 1.82; 21 deaths (Shannon *et al.* 2005) and among 5,275 glass wool workers in the European cohort (SMR = 1.18, 95% CI = 0.98 to 1.40; 127 deaths) (Sali *et al.* 1999).

Respiratory effects: morbidity studies

Several studies have evaluated adverse respiratory effects and exposure to glass wool fibers; these include studies measuring respiratory symptoms, lung abnormalities (monitored by chest radiographs), and pulmonary function. The findings from IARC (1998) are summarized, and studies published after the IARC (1988) review on exposures specific to glass fibers are described in detail.

The IARC (1988) review stated that numerous studies have reported that exposure to SVF causes irritation and inflammation of the upper respiratory tract. Bronchitis was also associated with exposure to SVFs in one study. Abnormalities on chest X-rays were reported in some (Nasr *et al.* 1971, Valentin *et al.* 1977), but not all studies (Wright 1968). Pathological changes in the lung (parenchymal involvement or pulmonary fibrosis) or respiratory distress were reported in workers with prolonged exposure to glass fiber in one study (Chiappino *et al.* 1981), but not in another study (Gross *et al.* 1971).

No effects on pulmonary function were found in a study of 6 workers exposed to glass wool or rockwool or in two studies of sheet-metal workers (Bjure *et al.* 1964, Hill *et al.* 1984, Hill *et al.* 1973, Sixt *et al.* 1983)

Moulin *et al.* (1988a) conducted a respiratory health assessment of 2,024 workers in three glass wool (1,041 from Plant A) and two rock wool production plants in France. A standardized questionnaire that covered occupational history, smoking habits, respiratory symptoms, and upper airway irritation was administered by industrial physicians. After adjusting for age and current smoking, significantly elevated ORs related to exposure to fibers were observed for cough, phlegm, and symptoms of the pharynx-larynx among workers at Plant A, but not among workers at the other two glass wool plants. ORs for symptoms of the pharynx-larynx (non-significantly) and for sinus and nasal cavity complaints (e.g., sinusitis, nasal congestion, and nosebleed) (significantly) increased with exposure duration ($P = 0.02$); however, no exposure response was observed for cough and phelgm. IARC (2002) reported that a nested case-control study (Moulin *et al.* 1987, published in French) did not confirm these results

Hunting and Welch (1993) investigated the occurrence of lung disease among sheet metal workers from the United States and Canada exposed to asbestos and fiberglass. The workers were selected from a larger study of workers with 20 years of experience with high use of fiberglass. The selection criteria for this study were workers who had participated in medical screening, worked in the sheet metal industry for at least 70% of their working career (or removal for 40% of their career) and were not welders for more than 20% of their career. Occupational exposure history was obtained by telephone interview for 333 workers (out of 407 who met the selection criteria), and cumulative exposure models were developed for high, medium, and low intensity exposure to fiberglass. In multiple logistic regression analyses, smoking, years of asbestos exposure and high intensity exposure to fiberglass (OR = 2.28, 95% CI = 1.07 to 4.86) were associated with chronic bronchitis risk, but only smoking and welding were risk factors for obstructive lung disease.

Kilburn and Warshaw (1991) investigated respiratory effects in 175 fiberglass production workers (12 women and 163 men) from a group of 500 U.S. workers who underwent medical examination. Most of the workers (137/175, 78%) reported a history of asbestos exposure and 38 workers were identified without known asbestos exposure; however, all had worked in a facility where ovens insulated with asbestos were cleaned, repaired, dismantled, and rebuilt. Chest radiographs, lung function measurements, and occupational and medical histories were taken. Pulmonary flows and volumes were adjusted for age, height, ethnicity, and smoking. Chest radiographs revealed small, irregular opacities in 31 men; 16.8% (23/137) of the workers exposed to asbestos and fiberglass, and 21% (8/38) of the workers exposed only to fiberglass. After adjusting for age and smoking, workers with abnormal radiographs (31/175) had greater functional pulmonary impairment than workers with normal radiographs (63/175). [No unexposed control group was included in this study.] The authors concluded that it was possible that the men who did not report exposure to asbestos were actually exposed since they shared a similar air environment, and thus the effects of fiberglass exposure could not be estimated independently of the effects from asbestos exposure.

Kilburn *et al.* (1992) examined pulmonary effects in 284 (182 men and 102 women) of 500 workers (end-users) who had worked for at least 20 years and completed medical examinations. The workers were employed in fiberglass sheeting and rotary spun fiberglass insulation. Pulmonary effects were determined using spirometry, lung volumes, chest radiographs, and occupational questionnaires. Air sampling showed that 49% to 83% of the fibers had diameters < 5 μm and 23% to 71% were < 3 μm; no asbestos fibers were identified. Chest radiographs revealed abnormalities in 43 workers (17 reported previous exposures to asbestos and 26 without reported exposure to asbestos). Pulmonary function was reduced in the workers with abnormalities (detected by radiographs) attributed to glass fiber exposure compared with workers without abnormalities and who were not exposed to asbestos. [There was no unexposed control group in this study.] The authors concluded that exposure to commercial rotary spun fiberglass used for insulating appliances appeared to produce pulmonary effects similar to asbestosis.

Hughes *et al.* (1993) also conducted a study of SVF workers at 7 plants (5 fibrous glass and 2 mineral wool manufacturing plants) in the United States. [These plants might be the same plants studied by Marsh and colleagues.] Workers underwent a chest X-ray (1,449), interview, and spirometry (1,030). Comparison (blue collar) workers were identified for each plant from the communities where the plants were located and participated in the spirometry (386), interview, and chest X-ray (305, no radiographs were available for comparison workers for 2 plants). The prevalence of respiratory symptoms (such as chronic bronchitis and cough) was higher in 3 of the 7 plants (1 glass and 2 mineral wool) than the comparison group. Among SVF workers, there were significant differences in pulmonary function (spirometric measurements) across the plants (highest for the very fine fiber plant); however, when asthmatic workers or workers with previous chest surgery were omitted from the analyses, no significant differences in pulmonary function were observed compared with the comparison group. The prevalence of small opacities (detected by radiographs) was higher among SVF workers (23/1435) than the comparison groups (2/305), and most (98%) of the opacities were found at two glass fibers plants with the highest average and cumulative exposures; one of these plants made small fibers. Analyses of all workers (controlling for film quality, smoking, and age) found a significant association for opacities with cumulative exposure, average exposure, and time in job, although only duration of exposure was significant after allowing for plant effect. Phase two of the study evaluated workers (157) at the two plants with the higher prevalence of opacities using pre-employment radiographs of each worker as the comparison; none of the workers with pre-employment radiographs had participated in the main part of the study. No significant differences in opacities were found between pre-employment and workers films, and the prevalence of opacities was not significantly related to any exposure indices in regression analyses.

Guber *et al.* (2006) reported a case of pulmonary fibrosis in a patient with exposure to glass wool fibers; the patient denied exposure to asbestos and did not smoke. Fibers with a chemical composition consistent with typical glass wool insulation were identified in sputum and biopsy samples.

Abbate *et al.* (2006) investigated changes in the respiratory system induced by occupational exposure to production dust from glass fiber-reinforced plastics. This study included 29 male subjects with a mean length of employment of 11 years. Heavy smokers (> 15 cigarettes/day) were excluded from the study. The subjects were given a medical examination, chest X-rays, and spirometric and other tests. Bronchoalveolar lavage fluid was submitted for microscopic and biochemical analysis. The respiratory function tests confirmed obstructive syndromes in the workers. There were qualitative and quantitative alterations of the alveolar macrophages and evidence of intense and active phlogosis (external inflammation). Biochemical analysis indicated an increase in protein content that was associated with a significant decrease in glutathione, suggesting alterations of the lung oxidant/antioxidant status. Antioxidant enzymes (CAT and SOD) were increased 3- to 5-fold. Alterations of the cellular and humoral components of the pulmonary interstitium were identified as acute alveolitis.

Other effects

Several studies have also evaluated non-respiratory effects and exposure to glass wool. In the cohort mortality studies, no significant increases in SMRs from non-malignant diseases were observed in the latest update of the U.S. workers (Marsh *et al.* 2001, Stone *et al.* 2004), glass wool workers in the European cohort (Sali *et al.* 1999) or in the Canadian cohort (Shannon *et al.* 2005). In an earlier update of the U.S. glass wool cohort (16,661 workers followed until 1985), a significantly increased SMR for nephritis and nephrosis was observed (SMR = 1.46, 56 deaths, $P < 0.01$) (Marsh *et al.* 1990). In a case-control study of glass wool workers from three plants (Newark, Ohio, Kansas City, Kansas, and Santa Clara, California) in the U.S. cohort assembled by Marsh, no association between exposure to respirable fibers and mortality from nephritis or nephrosis was reported. This study used two case-control analyses that evaluated deaths from nephritis or nephrosis as the underlying cause only (15 deaths) or underlying and contributing cause (47 deaths) (Chiazze *et al.* 1999).

IARC (2002) also reviewed several morbidity studies showing an association between mineral fiber exposure and dermal irritation and skin disease. One of these studies

reported that 25% of 259 workers in a manufacturing and processing plant for mineral wool insulation presented with a skin disease that was attributed to an allergy related to MMVF additives. Other studies reported high incidences of skin and eye irritation or positive patch tests with mineral fibers among construction workers or workers investigated for sick building syndrome.

5.4.2 Experimental animals

Toxic effects in experimental animals that are potentially important to the carcinogenic process include inflammation and fibrosis (IARC 2002). These effects are commonly graded according to the Wagner scale (Table 5-3). Other effects, such as genotoxic or mitogenic affects are discussed in Section 5.5 as they relate to potential mechanisms of carcinogenicity.

Table 5-3. Wagner grading scale for lung pathology

Description	Wagner score	Pathology
Cellular change		
Normal	1	No lesion
Minimal	2	Macrophage response
Mild	3	Bronchiolization, inflammation
Fibrosis		
Minimal	4	Minimal fibrosis
Mild	5	Linking of fibrosis
Moderate	6	Consolidation
Severe	7	Marked fibrosis and consolidation
	8	Complete obstruction of most airways

Source: Hesterberg *et al.* 1993

Studies with MMVF10 and MMVF11 in F344 rats exposed 6 hours/day, 5 days/week for up to 24 months have shown exposure-dependent responses in lung pathology that peaked at a Wagner score of 3 (Hesterberg *et al.* 1993). In this same study, a Wagner score of 4 was observed in rats exposed to chrysotile asbestos for only 3 months.

Cullen *et al.* (2000) reported on the pathogenicity of 104E-glass fibers, code 100/475 microfibers, and amosite asbestos in Wistar rats exposed 7 hours/day, 5 days/week for one year. Fibrosis (Wagner score of 4) was evident in four rats exposed to 104E fibers

after the 12-month exposure period, but the lesions were small and only 0.3% of the lung parenchyma was involved. In the nine animals that survived for another 10 to 12 months without further exposure, significant areas of advanced fibrosis and bronchoalveolar hyperplasia were evident. Instead of Wagner scores, the authors reported the mean level of advanced fibrosis as the percentage of lung area affected. The values were 0.08% (controls), 0.2% (100/475 glass), 8.0% (104E glass), and 7.6% (amosite). The authors noted that there were greater numbers of long fibers in the lungs of animals exposed to 104E glass for 12 months compared with the other fiber types.

Hesterberg *et al.* (1999, 1997) investigated the effects of inhalation exposure in Syrian golden hamsters. Animals were exposed for 6 hours/day, 5 days/week for periods of 13 to 52 weeks. MMVF10a, MMVF33, and amosite asbestos were used in the studies. Time-dependent increases in pathology were noted with Wagner scores after 52 weeks of 0 (controls), 2.3 (MMVF10a), 4.0 (MMVF33 and low-dose amosite), and 6.0 (high-dose amosite). McConnell *et al.* (1999) reported on a similar study design in Syrian golden hamsters exposed to these same test fibers for 78 weeks. The fibrosis index in hamsters exposed to MMVF10a or MMVF33 was not significantly different from controls but was significantly elevated in hamsters exposed to amosite.

Hesterberg *et al.* (2002) used a short-term assay to evaluate the toxicity of MMVF10, JM475, amosite asbestos and two new biosoluble glass wool fibers (JM902 and JM901F). MMVF10 and JM902 were tested concurrently, while JM901F, JM475, and amosite asbestos were tested in a separate study. Size-separated fiber samples were tested for lung biopersistence and their potential to induce persistent pulmonary inflammation in rats. Groups of 82 to 105 male F344 rats were exposed by nose-only inhalation for 6 hours/day for 5 days. The control groups included 45 to 55 rats exposed to filtered air. The geometric mean dimensions of the fibers were similar and the mean concentrations of WHO fibers ranged from 321 to 443 fibers/cm^3. In addition, intratracheal instillation biopersistence studies were conducted with JM902 fibers. Dissolution rate constants were measured *in vitro*. Histopathological effects were limited to fiber-containing microgranulomas and alveolar macrophage aggregation in rats exposed to JM902,

JM901F, or MMVF10 on recovery day 1. After 30 days recovery, no adverse symptoms were noted, while some inflammatory symptoms were still present in rats exposed to JM475 or amosite.

Bellmann *et al.* (2003) conducted a subchronic inhalation study in male Wistar rats to investigate the biological effects of E-glass microfiber, stone wool (MMVF21), and a new high-temperature application fiber (calcium-magnesium-silicate fiber). Results are reported here for the E-glass microfiber. Rats were exposed 6 hours/day, 5 days/week for 3 months to aerosol concentrations of approximately 15, 50, and 150 fibers/cm^3 (fiber length > 20 μm). For the E-glass microfiber, the highest gravimetric concentration was 17.2 mg/m^3. Recovery effects were studied during a 3-month postexposure period. The lung burden of the long fiber fraction of E-glass declined 38.4% after 3 months recovery. The estimated half-times were 55 to 157 days for WHO fibers and 57 to 63 days for fibers > 20 μm in length. Dose-dependent effects included an increase in lung weight in the mid- and high-dose groups at 1, 7, and 14 weeks after exposure. Biochemical analysis of bronchoalveolar lavage fluid indicated a significant increase in lactate dehydrogenase, β-glucuronidase, and total protein after 1 and 7 weeks in the mid- and high-dose groups; however, at 14 weeks, total protein was the only parameter that remained elevated. Cytokine analysis (TNF-α and IL-6) did not show any significant changes. Histopathological findings included accumulation of fiber-laden macrophages, bronchoalveolar hyperplasia, microgranulomas, and interstitial fibrosis in all exposure groups. The authors concluded that the effects induced by E-glass were more pronounced than those induced by the other fibers.

Bermudez *et al.* (2003) investigated toxicity of MMVF10a fiberglass in male F344 rats and Syrian golden hamsters using pleural dosimetry. Animals were exposed (nose-only) to a target concentration of 45 mg/m^3 for 4 hours/day, 5 days/week for up to 12 weeks. Animals were killed following 4 or 12 weeks of exposure or after 12 weeks of exposure followed by a 12-week recovery period. The geometric mean length and diameter of the fiber samples were 12.5 μm and 0.93 μm, respectively. Lung fiber burdens (calculated total number of fibers per lung, averaged over the three time points) were greater in rats

(50.1 × 10^6 fibers/lung) than in hamsters (6.4 × 10^6 fibers/lung). When lung fiber burdens were normalized based on lung surface area, rats had significantly higher lung burdens than hamsters. Fibers recovered from the lungs of both species were shorter and thinner than those in the aerosol. Lung fiber burdens decreased about 90% in hamsters following 12 weeks of postexposure recovery compared with 44% in rats. Average fiber burdens in the pleural compartment were about the same in rats and hamsters but were at least three orders of magnitude lower than found in the lung. When normalized based on surface area, pleural fiber burdens > 5 μm in length were significantly higher in the hamster at 12 weeks of exposure. Fibers in the pleural compartment were longer than those found in the lung but were about the same diameter. Mild pulmonary inflammation was observed in both species and characterized by increased numbers of macrophages and neutrophils, and an increase in mesothelial cell replication. The neutrophil response was correlated with lung fiber burdens in the rat but not in the hamster. All the biochemical markers examined in the rat bronchoalveolar lavage fluid were elevated after 4 weeks exposure, and LDH and alkaline phosphatase levels remained elevated and unchanged through 12 weeks recovery. There were no significant increases in the biochemical markers of toxicity in bronchoalveolar lavage fluid in hamsters.

5.4.3 Cytotoxicity

Similar to the IARC (2002) review, this section is limited to studies that met several criteria, including: (1) the dose was expressed as number of fibers administered, (2) fiber length was specified so that false-negative results from preparations of short fibers could be excluded, (3) adequate documentation of fiber source was supplied, (4) studies involving instillation of fibers directly into the lungs were screened to exclude those with excessive doses, and (5) control fibers were used or different categories of fiber length were used.

One study used Chinese hamster ovary cells to assess cytostatic effects of MvL 901 glass fibers (Hart *et al.* 1994). Fibers with an average length of 25 μm inhibited cell proliferation to approximately 25% of control levels, whereas, fibers with an average length of 3.5 μm did not inhibit cell proliferation. A modest effect was also seen for fiber

thickness, with thinner fibers being more effective inhibitors of cell proliferation than thicker fibers. The authors noted that this study showed that long fibers were toxic *per se*, in addition to their ability to accumulate in the lung due to slower clearance rates.

Blake *et al.* (1998) assessed the ability of Code 100 glass fibers, at varying lengths, to inhibit lucigenin chemiluminescence and to cause release of lactate dehydrogenase from rat alveolar macrophages. A length-related toxicity was seen, with fibers of 17 μm and 33 μm showing similar high potency while fibers less than or equal to 7 μm showed markedly lower potency. The authors suggested that the increased toxicity of long fibers was due to frustrated phagocytosis leading to leakage of oxidants and enzymes from a macrophage trying to engulf a fiber.

Zeidler-Erdely *et al.* (2006) investigated the influence of fiber length on primary human alveolar macrophages. JM100 glass fibers were sorted into four length categories (8, 10, 16, and 20 μm). Macrophages were obtained by bronchoalveolar lavage of healthy, non-smoking volunteers and treated with three different concentrations of the sized fibers *in vitro*. Cytotoxicity was determined by monitoring cytosolic lactate dehydrogenase release and loss of function (decrease in zymosan-stimulated chemiluminescence). In contrast to the study in rats (Blake *et al.* 1998), human macrophages completely engulfed glass fibers of all length categories with no evidence of incomplete phagocytosis or length-dependent toxicity. All fiber length fractions exhibited equal cytotoxicity on a per fiber basis in a dose-dependent manner.

5.5 Genetic and related effects

This section reviews the available genetic and related effect studies for glass fibers, including those reviewed by IARC and those published subsequent to the IARC review. This review includes studies of oxidative and genetic damage (such as mutations, micronucleus formation, DNA damage) and also studies of related effects, such as production of reactive oxygen species and changes in gene expression. Some of the studies were designed to evaluate the effects of fiber characteristics (diameter and length and sometimes fiber composition) on the genotoxic endpoint. Some of the fibers used in these studies were used in animal cancer studies or were manufactured to be similar to a

fiber used in the animal studies. These include the special-purpose fibers (e.g. Mansville codes JM100, JM100/475) and insulation glass wool fibers (e.g., MMVF10, MMFV11 and Owens Corning general insulation fibers). However, as IARC noted, no studies are available that correlated genotoxic endpoints and pathogenic effects in the same experimental animal system.

5.5.1 Production of reactive oxygen species

The following sections discuss studies that investigated reactive oxygen species produced by exposure to glass wool. Although reactive oxygen species are not necessarily associated with genotoxicity, they may damage DNA or chromosomes. This section discusses studies conducted in cell-free systems, cultured cells, or experimental animals.

Cell-free system

The ability of glass wool to produce reactive oxygen has been studied in cell-free systems measuring guanine hydroxylation in DNA or deoxyguanosine, which indicates the formation of the hydroxyl radical, studies using the salicylate assay to measure hydroxyl radical formation, and studies measuring scission of plasmid DNA after incubation with glass wool. These studies are summarized in Table 5-4.

All of the guanine hydroxylation studies were positive; [however, most studies did not provide detailed information on fiber characteristics] (Adachi *et al.* 1992, Leanderson *et al.* 1988, Leanderson and Tagesson 1992). Glass wool and JM100 glass fibers induced hydroxyl radical formation in the presence of hydrogen peroxide (Maples and Johnson 1992). These authors reported a significant correlation between the capacity of natural fibers (asbestos and erionite) to initiate hydroxyl radical formation and tumor rates in rat i.p. studies or literature values for human mesothelioma mortality rates; however, no correlations were found with glass fibers. In another study, JM100/475 and an insulation glass wool fiber (MMVF10) did not induce hydroxyl radical formation; however, this study was conducted at a lower pH (3.9) than the Maples and Johnson study (neutral pH) and did not use hydrogen peroxide (Brown *et al.* 1998).

Several studies were conducted that reacted glass fibers with plasmid DNA and measured oxidative DNA damage to the plasmid (as assessed by a reduction in the percentage of

supercoiled DNA) (Brown *et al.* 1998, Donaldson *et al.* 1995b, Gilmour *et al.* 1995, Gilmour *et al.* 1997). All of these studies were negative. However, Gilmour *et al.* (1995, 1997) reported that MMVF10 and MMVF11 did have a detectable, although not statistically significant, effect on plasmid DNA. In contrast, there was significant free radical damage with amosite asbestos. There was no correlation between iron release from the fibers and free radical activity. Although the authors demonstrated that iron at the surface of asbestos fibers had a role in generating hydroxyl radicals, some fibers released large quantities of iron without causing free radical damage. Thus, the exact role of iron in fiber reactivity is not completely understood.

Table 5-4. Oxidative damage studies in cell-free systems

End point	Test system	Result	Fiber type (dose)	Fiber length & diameter (μm)	Reference
Guanine hydroxylation in DNA or deoxyguanosine (dG) or hydroxyl radical studies					
Hydroxylation of deoxyguanosine	Deoxguanosine	+	Glass wool (NR)	NR	Leanderson *et al.* 1988
8-OHdG formation (hydroxylation of guanine in DNA)	Calf thymus DNA	+	Glass wool (20 mg)	NR	Leanderson *et al.* 1988
8-OHdG formation (Hydroxylation of deoxyguanosine)	Calf thymus DNA	+	Glass wool (10 mg)	NR	Leanderson and Tagesson 1989
8-OHdG formation (Hydroxylation of deoxyguanosine	Calf thymus DNA	+	Glass wool (10 mg)	NR	Leanderson *et al.* 1989
8-OHdG formation (5.0 mg)	Calf-thymus DNA	+	Fiberglass	L = 16.8 D = 0.65	Adachi *et al.* 1992
Hydroxyl radical formation	hydrogen peroxide	+	Mansville code 100/SPF (1 mg/mL)	NR	Maples and Johnson 1992
Hydroxyl radical formation	hydrogen peroxide	+	Owens Corning glass wool/IGW (1 mg/mL)	NR	Maples and Johnson 1992

End point	Test system	Result	Fiber type (dose)	Fiber length & diameter (μm)	Reference
Hydroxyl radical formation	Cell-free system	–	Mansville code 100/475/SPF 8.24×10^7 fibers	NR	Brown *et al.* 1998
Hydroxyl radical formation	Cell-free system	–	MMVF10/IGW 8.24×10^7 fibers	NR	Brown *et al.* 1998
Plasmid DNA scission studies					
Reduction of supercoiled DNA	Plasmid DNA	–	Code 100/475/ SPF (46.25×10^6/mL WHO fibers[a])	NR	Brown *et al.* 1998
Reduction of supercoiled DNA	Plasmid DNA	–	MMVF10/IGW (46.25×10^6/mL WHO fibers[a])	NR	Brown *et al.* 1998
Reduction of supercoiled DNA	Plasmid DNA	–	MMVF10/IGW (46.5×10^6/mL WHO fibers[a])	NR	Gilmour *et al.* 1997
Reduction of supercoiled DNA	Plasmid DNA	–	MMVF10 MMVF11/IGW (30.8×10^6/mL WHO fibers[a])	NR	Donaldson *et al.* 1995b
Reduction of supercoiled DNA	Plasmid DNA	–	MMVF10 MMVF11/IGW (61.7×10^6/mL WHO fibers[a])	NR	Gilmour *et al.* 1995

+ = positive;– = negative; L = length, D = diameter; NR = not reported in this study; SPF = Special purpose glass fibers; IGW = Insulation glass wool fibers.
[a]WHO fibers are longer than 5 μm and less than 3 μm in diameter, with aspect ratio (ratio of fiber length to fiber diameter) > 3, defined as respirable fibers.

Cultured cells

Most studies have reported that glass fibers cause oxidative damage in cultured cells. These studies have used different types of fibers (varying in length and diameter) and assessed oxidative damage by different endpoints. These studies are summarized in Table 5.5.

Superoxide production induced by glass fibers (Code 100/475 - either uncoated or coated with rat immunoglobulin (IgG), was studied in rat alveolar macrophages (Donaldson *et al.* 1995b, Hill *et al.* 1996), and glass fiber code 100 was studied in rat alveolar macrophages and hamster alveolar macrophages (Hansen and Mossman 1987, Mossman

and Sesko 1990). Dörger *et al.* (2000, 2001) investigated the responses of rat alveolar and peritoneal macrophages and hamster alveolar macrophages exposed to MMVF10. All studies except Dörger *et al.* (2000, 2001) reported increased superoxide production in alveolar macrophages exposed to glass fibers. IgG opsonization of Code 100/475 did not increase superoxide production.

Gilmour *et al.* (1997) reported that intracellular glutathione levels were significantly decreased in rat alveolar macrophages exposed to MMVF10; however, glutathione depletion was not related to free radical activities of the fibers (see "*in vivo studies*" in Section 5.5.1). The authors concluded that the decreased glutathione was likely a result of exportation as a stress response rather than a direct free radical oxidation of glutathione. Wang *et al.* (1999b) reported that both a long glass fiber (GW1) and a microfiber (MG1) increased superoxide anion (as measured by cytochrome C reduction) and hydrogen peroxide production, and depleted glutathione in guinea-pig alveolar macrophages. GW1 induced levels of hydrogen production similar to that of asbestos (chrysotile). Glass wool also increased hydrogen peroxide production in human polymorphonuclear leukocytes (Leanderson and Tagesson 1992).

Nishiike *et al.* (2005) investigated the effects of asbestos and SVFs on nitrosothiol formation and glutathione levels in the murine macrophage cell line (RAW264.7). J774 cells were also used in some experiments. Glass wool and chrysotile asbestos significantly increased nitric oxide and superoxide anion production and decreased glutathione levels in RAW264.7 cells. *S*-nitrosothiol formation was increased in both cell lines by all fiber types tested.

Brown *et al.* (1986) reported that there was no increase of malondialdehyde production (an indicator of lipid peroxidation) in human A549 cells exposed to 50 $\mu g/cm^2$ glass fibers; however, malondialdehyde was significantly increased in cell cultures treated with crocidolite asbestos. MMVF10 and MMVF11 (insulation glass wool fibers) caused dose-dependent increases in reactive oxygen species in human polymorphonuclear cells (Luoto *et al.* 1997). Fibers of different lengths (MG1, a short micro fiber; and GW1, a longer glass fiber) induced reactive oxygen species in human monocytes (Ohyama *et al.* 2000)

and guinea-pig alveolar macrophages (Wang *et al.* 1999b); however, the longer fiber (GW1) was more effective in inducing reactive oxygen species than the shorter fiber (MG1) in human monocytes. Ruotsalainen *et al*. (1999) reported that fiber size did not appear to be important in inducing reactive species in human polymorphonuclear leukocytes; dose-dependent increases in production of reactive oxygen were induced by two glass fibers of different sizes. A similar observation was observed between fiber lengths of other types of fibers (e.g., refractory ceramic fibers, rock wool). However, the glass wool fibers in the Ruotsaleinen *et al.* (1999) study appeared to have a more heterogeneous size distribution than the GW1 and MG1 fibers in the Ohyama *et al*. study (2000). Ruotsalainen *et al*. (1999) also included other types of synthetic fibers and suggested that fiber composition might mediate production of reactive oxygen species because the amount of ROS production differs according to the fiber type of similar dimensions.

Zoller and Zeller (2000) investigated the potential for four SVFs (including glass wool Code A) and two natural mineral fibers (crocidolite and erionite) to induce ROS in a differentiated human promyelocytic cell line (HL-60-M cells). ROS production was measured by lumino-enhanced chemiluminescence. The influence of fiber preincubation in unbuffered saline also was investigated. Cell cultures exposed to 250 μg of glass fibers showed increased chemiluminescence; however, decreased ROS-generating potential was observed after preincubation in saline for 4 weeks. The authors thought that the decreased ROS-generating potential of Code A fibers was likely due to surface alterations (leaching and initiation of dissolution).

In contrast, to the cell-free studies using calf-thymus DNA, Murata-Kamiya *et al*. (1997) reported no increase in 8-OHdG formation when the DNA of a reticulum-cell sarcoma line (J774) was incubated with glass fibers (100 μg/mL).

Table 5-5. Oxidative damage in cultured cells

End point	Test system	Result	Fiber type (Dose)	Fiber length & diameter (μm)	Reference
Superoxide production	Rat alveolar macrophages	+	Mansville Code 100/475/SPF (3 million fibers)	L = > 5	Donaldson *et al.* 1995b
Superoxide production	Rat alveolar macrophages	+	Mansville Code 100/475/SPF (12.5–2000 μg) 121,742 WHO fibers/μg	L = > 5	Hill *et al.* 1996
Superoxide production	Rat alveolar macrophages	+	Mansville Code 100/SPF (5 μg/cm^2)	L = 1–100 D = 0.2–2.9	Hansen and Mossman 1987, Mossman and Sesko 1990
Intracellular glutathione	Rat alveolar macrophages	+	MMVF10 (8.2×10^6 fibers/mL)	NR	Gilmour *et al.* 1997
Superoxide production	Hamster alveolar macrophages	+	Mansville Code 100/SPF (0.01–20 μg/cm^2)	L = 1–100 D = 0.2–2.9	Hansen and Mossman 1987, Mossman and Sesko 1990
Superoxide anion production (cytochrome C reduction) Hydrogen peroxide production	Guinea-pig alveolar macrophages	+ +	MG1 micro glass fibers, (200 μg/mL)	L = 3.0 D = 0.24;	Wang *et al.* 1999b
Superoxide anion production (cytochrome C reduction) Hydrogen peroxide production	Guinea-pig alveolar macrophages	+ +	GW1 glass wool fibers (200 μg/mL)	L = 20 D = 0.88	Wang *et al.* 1999b
Superoxide anion production (cytochrome C reduction)	Rat and hamster alveolar macrophages	–	MMVF10 (12 μg)	L = 16.3 D = NR	Dörger *et al.* 2000
Superoxide anion production (cytochrome C reduction)	Rat alveolar and peritoneal macrophages	–	MMVF10 (100 μg/mL)	L = 16.3 D = NR	Dörger *et al.* 2001
Nitric oxide and superoxide anion production	Murine RAW264.7 and J774 cells	+	Glass wool (100 μg)	L = 20 D = 0.88	Nishiike *et al.* 2005
Malondialdehyde	Human A549 cells	–	Glass fibers	NR	Brown *et al.*

End point	Test system	Result	Fiber type (Dose)	Fiber length & diameter (μm)	Reference
production			(50 μg/cm^2)		1986
Reactive oxygen species production	Human polymorphonuclear leukocytes	+	MMVF10, (100 μg/mL)	L=23.21, D=1.42;	Luoto *et al.* 1997
Reactive oxygen species production	Human polymorphonuclear leukocytes	+	MMVF11 (200 μg/mL)	L = 15.65 D = 1.12	Luoto *et al.* 1997
Reactive oxygen species production (chemiluminescence)	Human polymorphonuclear leukocytes	+	Two glass wool fibers (2 and 3) of different chemical composition (100–1000 μg/mL)	D = < 5 L = 10–50 (~70% of fibers); ~25 % fibers 2 were > 50, and ~25% of fiber 3 were ,10.	Ruotsalainen *et al.* 1999
Reactive oxygen species production (chemiluminescence)	Human monocytes	+	MG1 micro glass fibers, (5×10^5 fibers)	L = 3.0 D = 0.24	Ohyama *et al.* 2000
Reactive oxygen species production (chemiluninescence)	Human monocytes	+	GW1 glass wool fibers (5×10^5 fibers)	L = 20 D = 0.88	Ohyama *et al.* 2000
Reactive oxygen species production (chemiluninescence	Human HL-60 cells	+	Code A glass wool (250 μg)	L = >5 (87.5%) D = <1 (84%)	Zoller and Zeller 2000
Hydrogen peroxide production	Human polymorphonuclear leukocytes	+	Glass wool	NR	Leanderson and Tagesson 1992
8-OHdG formation	Human polymorphonuclear leukocytes	+	Glass wool (50–1,000 μg/mL)	NR	Leanderson and Tagesson 1992
8-OHdG formation	J774 cells Reticulum cell sarcoma line	–	Glass fibers (100 μg/mL)	L = 12.8 D = 0.54	Murata-Kamiya *et al.* 1997

+ = positive ; – = negative , NR = not reported
L=length, D=diameter
SPF = Special purpose glass fibers; IGW = Insulation glass wool fibers

In vivo

Schürkes *et al.* (2004) investigated the role of indirect (inflammation-driven) genotoxicity in fiber-induced carcinogenicity. Induction of the pre-mutagenic DNA-adduct 8-OHdG by MMVF11 or crocidolite asbestos (with and without reduced iron content) was measured and correlated with parameters of inflammation. Groups of female Wistar rats were injected i.p. with crocidolite (1 or 2 mg) or MMVF11 (14.7, 29.4, 50,

and 100 mg). Previous i.p. carcinogenicity studies with these fibers (Roller *et al.* 1996), indicated that 1 mg of crocidolite and 50 mg of MMVF11 were associated with a theoretical lifetime tumor risk of 25%. The two lower doses of MMVF11 were chosen to give comparable fiber numbers relative to crocidolite. All fiber suspensions were given in a single injection in a volume of 2 mL of PBS except the high dose for MMVF11, which was given in two injections. The control group was injected with 2 mL of PBS. There were significant comparable increases in 8-OHdG in the greater omentum for all fiber treatment groups. The percentage of macrophages and TNF-α secretion was significantly correlated with induction of 8-OHdG 10 weeks after treatment. The authors concluded that this study supported the hypothesis of persisting inflammation as an important parameter for fiber-induced mutagenesis.

Kováčiková *et al.* (2004) investigated the antioxidant status of the lung in male F344 rats administered stone wool or glass fibers by intratracheal instillation. Animals were exposed to 2 mg or 8 mg of fibers for 4 or 16 weeks. The high dose was administered in 4 doses at weekly intervals. All doses were administered in 0.2 mL of saline, and control groups were administered saline. The activity of superoxide dismutase, glutathione peroxidase, and total glutathione was measured in lung tissue and in cell-free fractions of bronchoalveolar lavage fluid. Ascorbic acid was measured in lung tissue. In rats exposed to glass fibers, there were no statistically significant differences in lung tissue except an increase in ascorbic acid in the group exposed for 4 weeks to 8 mg. Superoxide dismutase also was significantly decreased in bronchoalveolar lavage fluid from this group. Only mild dose-dependent histological alterations were seen in the exposed groups.

5.5.2 Genetic damage: prokaryotic systems

Manville Code 100 glass fiber (JM100) and code 110 coarse glass fiber (JM110) did not cause reverse mutations in *Salmonella typhimurium* TA1535 and TA1538 or in *Escherichia coli* B/r, WP2, WP2 *uvrA* and WP2 *uvrA polA* (Chamberlain and Tarmy 1977). These fibers differ in both length and diameter (code 110 are much longer and thicker than code 100) (See Table 5-6).

Table 5-6. Summary of prokaryotic studies

Test system	End point	Result	Fiber type/Fiber class (Dose)	Fiber length & diameter (μm)	Reference
Salmonella typhimurium TA1535, 15388	Reverse mutations (NR)	–	Manville Code 100 (JM100) SPF	L = 2.7 D = 0.12	Chamberlain and Tarmy 1977
Salmonella typhimurium TA1535, 15388	Reverse mutations (NR)	–	Manville Code 110 coarse glass fibers (JM110)	L = 26 D = 1.9	Chamberlain and Tarmy 1977
Escherichia coli B/r, WP2, WP2 *uvrA,* WP2 *uvrA polA*	Reverse mutations (1–1000 μg/plate)	–	Manville Code 100 (JM100) SPF	L = 2.7 D = 0.12	Chamberlain and Tarmy 1977
Escherichia coli B/r, WP2, WP2 *uvrA,* WP2 *uvrA polA*	Reverse mutations (1–1000 μg/plate)	–	Manville Code 110 coarse glass fibers (JM110)	L = 26 D = 1.9	Chamberlain and Tarmy 1977

L = length, D = diameter.
+ = positive;– = negative.
SPF = special purpose glass fibers; IGW = insulation glass wool fibers.

5.5.3 Genetic damage: mammalian in vitro *systems*

DNA damage, repair and cross linking

Several studies, using different types of glass fibers (which varied in fiber length and diameter) were conducted to evaluate whether glass fibers could damage DNA. Most of these studies assessed DNA damage by the single cell gel/comet assay and most studies were positive (See Table 5-7).

Zhong *et al*. (1997b) used the alkaline single cell gel/comet assay to compare DNA damage in Chinese hamster V79 cells with human embryonic lung fibroblasts (Hel 299 cells) exposed to Owens-Corning AAA-10 glass fibers (1.7, 3.4, 6.9, and 27.6 μg/cm^2). Significant DNA damage was reported in V79 cells at all four concentrations tested and in human embryonic lung fibroblasts (Hel 299 cells) at the three highest doses. Wang *et al*. (1999a) reported that both long glass wools fibers (GW1, length = 20 μm) and microfibers (MG1, length = 3 μm) induced DNA damage (as assessed by the comet assay), inhibited DNA repair and caused DNA-DNA intrastrand cross links in human epithelial cells. Cavallo *et al.* (2004) exposed human mesothelial cells (Me-T-5A) to four

concentrations of glass wool (1,2, 5 and 10 μg/cm^2 for 2 hours and measured DNA damage (as assessed by the comet assay) and oxidative DNA damage (assessed by the comet assay treated with Fpg [formamidopyrimidine DNA-glycosylase]). Glass wool caused non-significant dose-related increases of direct DNA damage and a slight increase in oxidative damage at the highest dose. Kováčiková *et al.* (2004) isolated and cultured alveolar macrophages and type II cells from F344 rats. After a 20-hour incubation, the cells were exposed to various concentrations of glass fibers, rockwool, wollastonite, and amosite. The comet assay was used to detect DNA damage. DNA strand breaks were enhanced in both cell types by exposure to all fibers in a dose-dependent manner. The highest level of damage was seen in cells exposed to amosite. Type II cells exposed to glass fibers showed the lowest level of damage.

Table 5-7. DNA damage and repair in mammalian cells

End point (dose)	Test system	Result	Fiber type/class (Dose)	Fiber length & diameter (μm)	Reference
DNA damage (comet assay)	Chinese hamster V79 cells	+	Owens-Corning AAA-10 (1.7–27.6 μg/cm^2)	L = 2.0, D = 0.18	Zhong *et al.* 1997b
DNA damage (comet assay)	Human embryonic lung fibroblasts (Hel 299)	+	Owens-Corning AAA-10 (1.7–27.6 μg/cm^2)	L = 2.0, D = 0.18	Zhong *et al.* 1997b
DNA damage (comet assay)	Human epithelial cells (A549)	+	MG1 micro glass fibers, (40 μg/cm^2)	L = 3.0, D = 0.24	Wang *et al.* 1999a
DNA damage (comet assay)	Human epithelial cells (A549)	+	GW1 glass wool fibers (40 μg/cm^2)	L = 20, D = 0.88	Wang *et al.* 1999a
DNA damage (comet assay)	Human mesotheial cells (MeT-TA)	+/–	Glass wool; 1–10 μg/cm^2 (0.5 × 10^3 fibers/μg, WHO[a] = 0.19 × 10^3 fibers/μg, WHO < 20 μm = 014 × 10^3 fibers/μg)	L = 57.3, D = 4.3	Cavallo *et al.* 2004
Oxidative DNA damage (comet assay with Fpg enzyme)	Human mesotheial cells (MeT-TA)	+/–	Glass wool; 1–10 μg/cm^2 (0.5 × 10^3 fibers/μg, WHO[a] = 0.19 × 10^3 fibers/μg, WHO < 20 μm = 014 × 10^3 fibers/μg)	L = 57.3, D = 4.3	Cavallo *et al.* 2004
DNA damage (comet assay)	F344 alveolar macrophages and type II cells	+	Glass fibers: 1–15 μg/cm^2	NR	Kovacikova *et al.* 2004
DNA repair	Human epithelial cells (A549)	+	MG1 micro glass fibers, GW1 glass wool fibers (40 μg/cm^2)	L = 3.0, D = 0.24	Wang *et al.* 1999a
DNA repair	Human epithelial cells (A549)	+	GW1 glass wool fibers (40 μg/cm^2)	L = 20, D = 0.88	Wang *et al.* 1999a
DNA-DNA intrastrand crosslinks	Human epithelial cells (A549)	+	MG1 micro glass fibers (40 μg/cm^2)	L = 3.0, D = 0.24	Wang *et al.* 1999a
DNA-DNA intrastrand crosslinks	Human epithelial cells (A549)	+	GW1 glass wool fibers (40 μg/cm^2)	L = 20, D = 0.88	Wang *et al.* 1999a

L = length; D = diameter; + = positive; – = negative, NR = not reported.

[a]WHO fibers are longer than 5 μm and less than 3 μm in diameter with aspect ratio (ratio of fiber length to fiber diameter) > 3, defined as respirable fibers.

Chromosomal or chromatid-related effects

It has been proposed that mineral fibers, including asbestos and synthetic fibers, can enter cells and physically interfere with chromosome segregation during mitosis, possibly resulting in aneuploidy and chromosomal translation. Numerous studies have been conducted to evaluate nuclear abnormalities (including micronuclei and polynuclei) and chromosomal aberrations (including polyploidy and structural aberrations). There has also been one study evaluating sister-chromatid exchange. Many of these studies evaluated the effect of fiber characteristics (e.g., composition, length, and diameter) on the genotoxic endpoint. The results from these studies are summarized in Table 5-8.

Hart *et al.* (1994) evaluated the effects of fiber length, fiber diameter, and composition of asbestos and vitreous fibers on cytotoxicity and induction of nuclear abnormalities (micronuclei and polynuclei) in Chinese hamster ovary cells. Cells were exposed to MvL 475 glass fibers of similar lengths but different diameters (ranging from 0.3 to 7 μm) and MvL 901 glass fibers of different lengths (ranging from 3.5 to 31 μm) and similar diameters. Fiber length but not fiber diameter (when calculated as the number of fibers/unit area) affected induction of nuclear abnormalities; longer fibers caused a greater percent of abnormalities than shorter fibers. Hesterberg *et al*. (1986) reported that unmilled glass fibers were more effective (almost 7-fold) in inducing micronucleus formation than milled fibers. Milling decreases fiber length, thus supporting the findings of Hart *et al.* that longer fibers are more potent inducers of micronuclei. Milling of fibers also affected phagocytosis, cytotoxicity, and transformation frequency. However, another study reported two microfibers (Manville 100 microfiber and Owens AAA-10 microfiber), but not Owens-Corning general insulation fibers, induced multinucleated and micronucleated cells in a concentration-dependent manner in Chinese hamster lung fibroblast cells (V79) (Ong *et al.* 1997). Most of the micronuclei were kinetochore positive, which is an indicator of aneuploidy. The microfibers were short and thin, whereas, the general insulation fibers were thicker and longer. Zhong *et al*. (1997a) also reported that Owens AAA-10 microfibers induced micronuclei in Chinese hamster lung fibroblasts (V79 cells). Significant concentration-related increases in frequencies of micronucleated and multinucleated cells were observed when the cells were exposed to concentrations of 1.7 to 27 $\mu g/cm^2$.

Thin glass wool fibers induced bi-and-multinucleated cells in rat liver cells, human primary mesothelial cells (PL-102), and an immortal, non-tumorigenic human mesothelial cell line (MeT-5A). Significant increases in the percentage of binucleated cells were observed at all doses (1, 2, 5 μg/cm^2) in the two types of human mesothelial cells but only at the highest dose in rat liver cells. Thin glass fibers appeared to be as effective as asbestos (when doses were expressed as the number of fibers per culture area) in inducing binucleated cells in human mesothelial cells. Milled glass wool caused significant increases in binucleated cells in MeT-5A cells (highest dose only) but not in PL-102 or rat liver cells (Pelin *et al.* 1995).

Sincock *et al*. (1982) reported that fine glass fibers (Mansville code 100) but not thick glass fibers (Mansville code 110) caused chromosomal aberrations (breaks and rearrangements) in Chinese hamster ovary cells (CHO). However, a respirable fraction of the thick glass fiber (but not the total sample) caused a significant increase in chromosomal aberrations (chromatid and isochromatid gaps) in Chinese hamster V79-4 cells in another study (Brown *et al.* 1979). Koshi *et al.* (1991) tested three glass fibers (Mansville Codes 100, 104 and 108A) of different fiber dimensions for chromosomal aberrations in Chinese hamster lung cells. None of the fibers caused significant increases in structural chromosome aberrations but all three types of fibers caused an increase in polyploidy; however, the thinner fibers (codes 100 and 104) caused increases at lower doses (10 μg/cm^2) than the thicker fiber (code 108A). In general, the clastogenic activity of glass fibers was mild compared with that of asbestos. An increase in structural chromosome aberrations was observed in human embryo lung cells treated with a microfiber (MG1) and a glass wool fiber (GW1) (Wang *et al.* 1999a).

Two insulation glass wool fibers (MMVF10 and MMVF11) did not induce anaphase or telophase aberrations (as assessed by lagging chromatin, bridge or asymmetric segregation) in rat pleural mesothelial cells when exposed to less than 2.5 x 10^5 Stanton fibers/cm^2 (length < 8 μm and diameter ≤ 0.25 μm), which are poorly represented in MMVF10 and MMVF11 fibers (Yegles *et al.* 1995).

Casey *et al*. (1983) reported that neither coarse glass nor fine glass caused sister chromatid exchange in CHO-K1 cells, human fibroblast (primary cells) or human

lymphoblastoid cells. However, both cell types caused mitotic delay (as measured by the number of second metaphase cells) in CHO-K1 cells, and human fibroblasts; the fine glass fibers caused a greater inhibition than the coarse glass fibers.

Table 5-8. Chromosomal or chromatid-related effects

End point (dose)	Test system	Result	Fiber type/class (Dose)	Fiber length & diameter (μm)	Reference
Nuclear abnormalities (Micronuclei and ploidy)	Chinese hamster ovary cells	+ No diameter dependent differences	Diameter study Five fibers of MvL475 glass (codes 90, 108, 110, 112) with diameters/SPF NA	D = 0.3–7 L = 16–27	Hart *et al.* 1994
Nuclear abnormalities (Micronuclei and ploidy)	Chinese hamster ovary cells	+	Length study Eight subpopulations sized selected from MvL 901/IGW NA	L = 3.5–31.4 D = 0.5–1.3	Hart *et al.* 1994
Micronuclei	Chinese hamster V79 cells	+	Owens-Corning AAA-10 (1.7-27.6 μg/cm^2)	L = 2.0 D =0.18	Zhong *et al.* 1997a
Micronuclei	Chinese hamster V79 cells	+	Owens-Corning AAA-10, (10-80 μg/mL)	L = 2.0 D = 0.18	Ong *et al.* 1997
Micronuclei	Chinese hamster V79 cells	+	Manville100 microfiber (10-80 μg/mL)	L = 3.5 D = 0.2	Ong *et al.* 1997
Micronuclei	Chinese hamster V79 cells	–	General purpose Building insulation/IGW 10-160 μg/mL	L = 98 D = 7.3	Ong *et al.* 1997
Micronuclei	Syrian hamster embryo cells	+	Mansville Code 100 (unmilled)/SPF (1 μg/cm^2)	L = 9.5 D = 0.13	Hesterberg *et al.* 1986
Bi- and multinucleated cells	Rat liver cells	+ (only at lowest dose)	Thin glass wool (1–5 μg/cm^2)	L = 3.8 D = 0.21	Pelin *et al.* 1995

End point (dose)	Test system	Result	Fiber type/class (Dose)	Fiber length & diameter (μm)	Reference
Bi- and multinucleated cells	Human mesothelial cells MeT-5A, PL102	+ +	Thin glass wool (1–5 μg/cm^2)	L = 3.8 D = 0.21	Pelin *et al.* 1995
Bi- and multinucleated cells	Rat liver cells	–	Milled glass wool (1–5 μg/cm^2)	NR Milling reduces fiber length	Pelin *et al.* 1995
Bi- and multinucleated cells	Human mesothelial cells: MeT-5A PL102	+ (highest dose) –	Milled glass wool (1–5 μg/cm^2)	NR Milling reduces fiber length	Pelin *et al.* 1995
Chromosomal aberrations	Chinese hamster V79-4 cells	– 110 T + 110 R	Mansville code 110 T 110 R (respirable)	D = 1.5–2.49 L = < 200	Brown *et al.* 1979
Chromosomal aberrations	Chinese hamster ovary cells (CHO) Primary human fibroblasts or lymphoblaoid lines	+ CHO – Human cells	Mansville code 100 (fine glass)/SPF	L = 2.7–26 D = 0.12–1.9	Sincock *et al.* 1982
Chromosomal aberrations	Chinese hamster ovary cells (CHO)	– CHO – Human cells	Mansville code 110 (coarse glass)	L = 2.7–26 D = 0.12–1.9	Sincock *et al.* 1982
Chromosomal aberrations (structural)	Chinese hamster lung cells	–	Mansville Codes 100, 104, 108A, 108B (10-300 μg/mL)	L: 90% < 5, 95% < 10 D: 100 0.29–0.32 104 0.39–0.53 108A 0.69–1.1 108B 1.2–2.4	Koshi *et al.* 1991

End point (dose)	Test system	Result	Fiber type/class (Dose)	Fiber length & diameter (μm)	Reference
Chromosomal aberrations (polyploidy)	Chinese hamster lung cells	+ 100, 104 all doses + 108A (100, 300)	Mansville Codes 100, 104, 108A (10, 30, 100,-300 μg/mL)	All fibers L: 90% < 5, 95% < 10 D: 100 0.29–0.32 104 0.39–0.53 108A 0.69–1.1	Koshi *et al.* 1991
Chromosomal aberrations	Human embryo lung cells	+	JFMRA[a] MG1 micro glass fibers (1.0 μg/cm^2)	L = 3.0 D = 0.24	Wang *et al.* 1999a
Chromosomal aberrations	Human embryo lung cells	+	JFMRA[a] GW1 glass wool fibers (1.0 μg/cm^2)	L = 20 D = 0.88	Wang *et al.* 1999a
Anaphase/telophase aberrations	Rat pleural mesothelial cells	–	MMVF10/IGW (6-10x10^3 fibers/μg)	L = 21.5 D = 0.55	Yegles *et al.* 1995
Anaphase/telophase aberrations	Rat pleural mesothelial cells	–	MMVF11/IGW (6-10x10^3 fibers/μg)	L = 16.7 D = 1.10	Yegles *et al.* 1995
Sister-chromatid exchange	CHO-K1, Human fibroblast (primary culture), Human lymphoblastoid cell line	–	Manville Code 100/SPF (0.01 mg/mL)	L = 2.7 D = 0.12	Casey 1983
Sister-chromatid exchange	CHO-K1, Human fibroblast (primary culture), Human lymphoblastoid cell line	–	Manville Code 110 coarse glass fibers (JM110) 0.01 mg/mL)	L = 26 D = 1.9	Casey 1983
Mitotic inhibition	CHO-K1, Human fibroblast (primary culture)	–	Manville Code 100/SPF (0.01 mg/mL)	L = 2.7 D = 0.12	Casey 1983
Mitotic inhibition	CHO-K1, Human fibroblast	+	Manville Code 110 coarse glass fibers	L = 26 D = 1.9	Casey 1983

End point (dose)	Test system	Result	Fiber type/class (Dose)	Fiber length & diameter (μm)	Reference
	(primary culture)		0.01 mg/mL)		

+ = positive;–= negative;+/–= slight effect at highest dose, non-significant dose-response (comet).
L = length, D = diameter.
[a]JFMRA= Japan Fibrous Material Research Association.

Cell transformation and transfection studies

The probable mechanism of asbestos-mediated carcinogenesis involves mutation and or activation, inhibition of tumor suppressor genes, and activation of transcription factors controlling the production of cytokines, cell transformation, and cell growth. A number of studies have investigated these endpoints in glass fibers and are reviewed in this section. The data are summarized in Table 5-9.

Gene amplification was determined by a Southern blot analysis of K-*ras*, H-*ras*, c-*myc*, and c-*fos* proto-oncogenes in 9 BALB-c-3T3 cell lines transformed by Owens-Corning AAA-10 glass fiber (Whong *et al.* 1999). Mutational spectra of the p53 tumor suppressor gene and the K-*ras* proto-oncogene were also determined. Gene amplification was found in 5 of 9 transformed cell lines for K-*ras*, 5 of 9 for c-*myc,* and 6 of 9 for c-*fos* proto-oncogenes, and all transformed cell lines showed H-*ras* gene amplification. Point mutations (transitions or transversions) were found in K-*ras* (exon 2) in 2 of 9 of the transformed cell lines and p53 (exons 2-5) in 6 of 9. The authors stated that the results show the possibility of genomic instability originating from chromosomal alterations induced by glass fibers, followed by gene amplification and/or gene mutations in proto-oncogenes and/or tumor suppressor genes.

Various types of glass wool fibers, including insulation glass wool and special-purpose glass wool fibers, have been shown to transform mammalian cells; however, transformation efficiency appeared to be affected by fiber length and diameter.

Gao *et al*. (1995) investigated cell transformation in NIH-c-3T3 cells and cytotoxicity in BALB/c-3T3 cells with three fibers: Owens-Corning insulation glass wool, Owens-Corning AAA-10 and JM100 fibers. All fiber types induced cytotoxicity (measured by relative cloning efficiency) and dose-related increases in cell transformation, and anchorage-independent growth of the transformed cells. The authors concluded that cell

transformation was inversely related to size, with the shortest fibers (AAA-10) having the highest transforming potency and the longest and thickest fibers (insulation glass wool) having the lowest potency. A similar relationship of fiber size and cytotoxicity (as measured by survival) was observed. In contrast to this, Hesterberg *et al*. (1986) reported that unmilled glass fibers induced greater toxicity and higher transformation efficiency than milled glass fibers in Syrian hamster embryo cells similar to that observed for micronuclei induction (see above). However, in the study reported by Gao *et al*. AAA-10 and JM100 fibers were also smaller in diameter besides being shorter than the insulation glass wool fibers, thus diameter size might also have contributed to differences in cell transformation. In another study in Syrian hamster embryo cells, thinner glass fibers (Mansville code 100) were more potent in inducing cell transformation and cytotoxicity (relative survival) than thicker glass fibers (Mansville code 110). Fiber length also affected transformation efficiency; transformation efficiency was reduced 10-fold when the length of the thin fibers was decreased from 9.5 μm to 1.7 μm, and was absent when the length was reduced to 0.95 μm (Hesterberg and Barrett 1984).

Glass fibers did not mediate transfection of plasmid and DNA replication in human MeT-5A mesothelial cells (Gan *et al.* 1993). Several asbestos fibers were positive in this assay.

Table 5-9. Gene mutation and amplification, cell transformation and DNA transfection studies

End point	Test system	Result	Fiber type/class (Dose)	Fiber length & diameter (μm)	Reference
Gene amplification, K-*ras*, H-*ras*, c-*myc*, and c-*fos*	9 Glass fiber-induced transformed BALB-c-3T3 cells	+	Owens-Corning AAA-10	L = 0.5–9 D = 0.08–0.8	Whong *et al.* 1999
Gene mutations: p53 and K-*ras*	9 Glass fiber-induced transformed BALB-c-3T3 cells	+	Owens-Corning AAA-10	L = 0.5–9 D = 0.08–0.8	Whong *et al.* 1999
Cell transformation, cytotoxicity	Syrian hamster embryo cells	+ (Code 100 more potent)	Mansville Code 100 (thin)/SPF Mansville Code 110 (thick) (0.1–10 μg/cm^2)	Code 100: L = 9.5 D = 0.13; Code 110: L = 10–140, D = 0.8	Hesterberg and Barrett 1984
Cell transformation	Syrian hamster embryo cells	+	Code 100 (unmilled) (1 μg/cm^2)	L = 9.5 D = 0.13	Hesterberg *et al.* 1986
Cell transformation	NIH-3T3, BALB/c-3T3 cells	+	Owens-Corning AAA-10 (1–150 μg/cm^2)	L = 0.5–0.9 D = 0.08–0.8	Gao *et al.* 1995
Cell transformation	NIH-3T3, BALB/c-3T3 cells	+	Mansville code 100/SPF (1–150 μg/cm^2)	L = 1–10 D = 0.05–0.5	Gao *et al.* 1995
Cell transformation	NIH-3T3, BALB/c-3T3 cells	+	Owen-Corning General purpose insulation/IGW	L = 25–200 D = 4–10	Gao *et al.* 1995
Transfection of plasmid, DNA replication	Human mesothelial cells (MeT-5A)	–	Glass fibers prepared by milling Pyrex wool filtering fiber/IGW (2, 20 μg/plate)	L = 30–60, D = 15–30	Gan *et al.* 1993

L = length; D = diameter; + = positive; – = negative; SPF = special purpose glass fibers; IGW = insulation glass wool fibers.

5.5.4 Genetic damage: mammalian in vivo *systems*

Bottin *et al*. (2003) exposed transgenic male *LacI* F344 rats (lambda LIZ, BigBlue) by nose only to CM 44 glass fibers (mean length = 5.0 μm and mean diameter = 0.37 μm) at

a concentration of 6.3 mg/m^3 (601 WHO fibers) for 5 days and examined mutations in lung DNA 1, 3, 14, 28, and 90 days following exposure. No significant differences in mutant frequencies between the exposed and control rats were observed. This fiber was also rapidly cleared from the lungs. Schürkes *et al.* (2004) investigated the induction of 8-OHdG in female Wistar rats exposed to MMVF11 (see Section 5.4.1.3), since the production of hydroxyl radicals in cells treated with fibers may result in the formation of pre-mutagenic DNA bases. MMVF11 (14.7, 29.4, 50, and 100 mg MMVF; diameter 0.08 μm to 4.20 μm, length 1.7 μm to 98.8 μm) was administered to female rats for 10 or 20 weeks. TNF-α released by macrophages from peritoneal lavages and the induction of 8-OHdG were measured. A dose of 14.7 mg resulted in significant increases in macrophages, while 100 mg resulted in decreased relative macrophage numbers. 8-OHdG was increased with increasing doses of MMVF. Percentages of macrophages correlated with the induction of 8-OHdG 10 weeks after treatment.

Topinka *et al.* (2006a) investigated mutagenesis and DNA damage in the lung of male homozygous λ-*lacI* transgenic F344 rats (Big Blue rats). Single doses of 1 or 2 mg, or four weekly consecutive doses of 2 mg of MMVF10 or rock wool fibers were administered by intratracheal instillation. No increase in mutant frequency was observed with MMVF10 fibers. However, DNA strand breaks (measured by the comet assay) were increased in macrophages and lung epithelial cells in treated rats. The rock wool fibers caused more extensive inflammation than glass wool fibers. There were only minor differences in the extent of inflammation in rats given single or multiple doses. There was some evidence of oxidative damage in rats that had received multiple doses of MMVF10 based on increased levels of malondialdehyde, a marker for oxidative stress, in lung tissue after 16 weeks.

5.6 Mechanisms of fiber carcinogenicity

The mechanisms of fiber-induced carcinogenicity are not completely understood, but several hypotheses have been proposed and are discussed below. The pathogenicity of fibers appears to depend on multiple factors, including fiber dimensions, location of deposition, biopersistence, uptake by macrophages or other target cells, migration into the interstitium and pleura, and induction of persistent inflammation and fibrosis. The German Commission for the Investigation of Health Hazards of Chemical Compounds in

the Work Area (DFG 2002) concluded that: "in principle, all kinds of elongated dust particles have the potential, like asbestos fibers, to cause tumors if they are sufficiently long, thin and durable *in vivo*." However, the definition of pathogenic fiber properties "sufficiently long, thin, and durable" is still under discussion. Clearance of the shorter fibers is similar to or faster than clearance of insoluble nuisance dusts (Bernstein 2006, Muhle et al. 1987); however, long fibers are not as easily cleared from the lungs and induce inflammation and fibrosis. (Davis and Cowie 1990). Since much of what is know about mechanisms of fiber carcinogenesis comes from studies of asbestos and other SVFs, the following discussion is not limited to glass fibers.

Nguea *et al* (2008) proposed that fiber-induced lung carcinogenesis could be explained by two different mechanisms relating to the physical properties of the fibers *in situ* and the effects of the fibers on macrophages (Figure 5-5). The potential for harm from inhaled fibers is dependent upon the following physicochemical properties: fiber dimension, biopersistence, surface reactivity and chemical composition. The fibers can directly interact with target cells (epithelial cells, meosthelial cells, fibroblasts) leading to an inflammatory response and/or genotoxicity. Alveolar macrophages provide an early immune response through phagocytosis of inhaled foreign bodies and amplification of the inflammatory response through the release of cytokines, reactive oxygen and nitrogen species, interleukins, mitogenic factors, and chemotactic factors. These inflammatory mediators would affect the local cell environment, leading to genotoxicity, proliferation and/or apoptosis. Depending on the properties of the fibers, incomplete phagocytosis (frustrated phagocytosis) can occur, leading to further amplification of the inflammatory response.

The potential mechanisms of fiber carcinogenesis have also been reviewed by others (Fubini and Fenoglio 2007, Hesterberg and Hart 2001, IARC 2002, Kane *et al.* 1996b, Nguea *et al.* 2008). The available reviews identify the following mechanisms as having important roles in the development of fiber-induced diseases: production and release of reactive oxygen species (ROS) and DNA damage, genotoxicity, chronic inflammation with release of cytokines and growth factors, cytotoxicity and increased cell proliferation, and co-carcinogenicity.

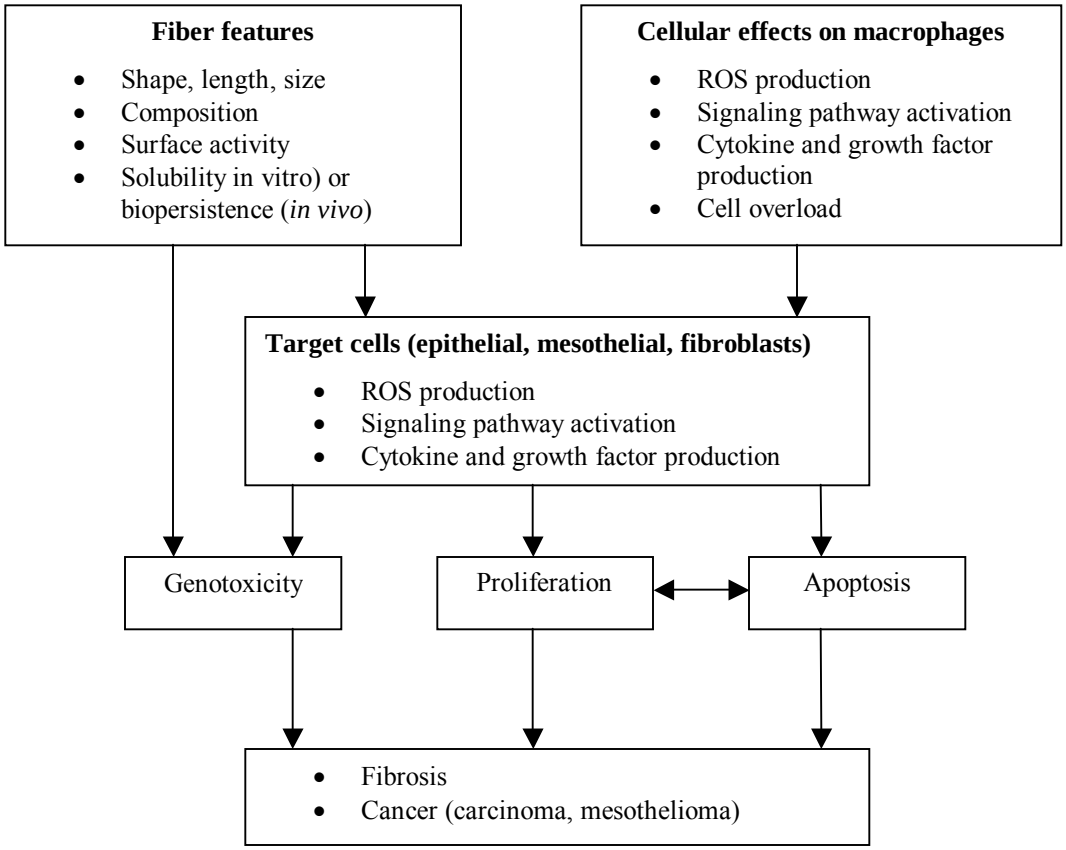

Figure 5-5. Mechanisms of fiber-induced toxicity and carcinogenicity

Adapted from Nguea 2008

5.6.1 Release of reactive oxygen species

Both natural fibers and SVFs have generated ROS and reactive nitrogen species (RNS) in cell-free or *in-vitro* model systems (Nguea *et al.* 2008). Proposed mechanisms include iron-catalysed generation of the hydroxyl radical in the presence of molecular oxygen, superoxide anion, or hydrogen peroxide or release of ROS (hydrogen peroxide, superoxide anion, nitric oxide, hydroxyl radical, peroxynitrite, or nitronium ions) from macrophages during incomplete phagocytosis (frustrated phagocytosis) of long fibers (Kane 1996a). Biopersistent fibers deposited in the lung cause chronic inflammatory reactions leading to generation of free radicals that mediate DNA damage and mutations in oncogenes, growth regulatory genes, and tumor suppressor genes. Thus, inflammatory reactions induced by persistent fibers in the lung are thought to be important genotoxic mediators that accelerate tumor development and progression (Nguea *et al.* 2008, Okada 2007) (see Section 5.6.2 for DNA damage).

Alveolar macrophages are the first line of defense in the alveolar environment and play a central role in recruiting and activating other inflammatory cells (Nguea *et al.* 2008). Rihn *et al.* (2000) demonstrated that inhaled crocidolite induced the release of ROS and RNS resulting in oxidation and nitrosylation of protein, and DNA, and lipoperoxidative damage of type II pneumocytes, fibroblasts, and mesothelial cells. Thus, cell injuries caused by release of these reactive species contribute to the pathogenesis of fiber-related lung disease and indicate that oxidative stress is a basic mechanism of the carcinogenic effect (Nguea *et al.* 2008). Zeidler-Erdely *et al.* (2006) showed that increasing the dose of JM100 glass fibers resulted in an increase in reactive species production by human alveolar macrophages. However, there was no effect of fiber length over the range of 8 to 20 μm. Ohyama *et al.* (2000, 2001) investigated the chemiluminescent response (an indicator of reactive species production) from human monocyte-derived macrophages exposed to glass wool, rock wool, refractory ceramic fibers, and others. These authors reported that there was a strong correlation between geometric-mean length and the ability to induce chemiluminescence for various fiber samples longer than 6 μm in length. There was no correlation with geometric-mean width; however, among two refractory fiber samples with similar lengths, the narrower width sample induced more chemiluminescence.

5.6.2 Chronic inflammation

A potential indirect mechanism of fiber carcinogenesis involves the release of cytokines and growth factors from inflammatory cells in the lungs (Kane 1996a). Macrophages are activated in response to particulates deposited in the lung resulting in increased release of ROS, chemical mediators, and cytokines. Cytokines sustain and amplify the inflammatory reaction. Thus, persistent fibers in the lung, interstitium, or subpleural connective tissue may cause a sustained chronic inflammatory reaction. A chronic imbalance between cytokines and growth factors may contribute to tissue injury and proliferation of epithelial and mesenchymal cells. Injury to the alveolar epithelial lining and basement membranes could enhance translocation of fibers and inflammatory mediators to the interstitium of the lung.

TNF-α and NF-κB

The roles of NF-κB and tumor necrosis factor-α (TNF-α), a mediator of inflammation that is also implicated in cell proliferation and apoptosis, have been the focus of several studies (Brown *et al.* 1999, Cullen *et al.* 1997, Fisher *et al.* 2000, Fujino *et al.* 1995, Gilmour *et al.* 1997, Murata-Kamiya *et al.* 1997, Schins and Donaldson 2000, Xie *et al.* 2000, Ye *et al.* 1999, Ye *et al.* 2001).

Results for production of TNF-α in response to exposure to glass fibers are variable. Fujino *et al.* (1995) tested the toxicity of several SVFs and natural fibers by measuring TNF-α production and release of lactate dehydrogenase (LDH) and β-glucuronidase (BGU) from rat alveolar macrophages *in vitro*. Cell cultures were incubated for 24 hours with the various fibers (100 μg/mL). There was a significant increase in TNF-α, LDH, and BGU in cell cultures exposed to glass fibers (specified as $SiO_2 \cdot Na_2O$ with a median length of 12.8 and diameter of 0.54 μm). The results were similar to the responses reported for chrysotile, crocidolite, and amosite. Murata-Kamiya *et al.* (1997) reported the TNF-α production was slightly increased (not significant compared with controls) in a murine macrophage cell line (J774 cells) exposed to 100 μg/mL of glass fibers for 18 hours. Cell cultures exposed to chrysotile asbestos showed a significant increase in TNF-α production. The glass fibers used in this study had the same geometric mean length and diameter as those tested by Fujino *et al.* (1995). Cullen *et al.* (1997) tested the effects of MMVF10, MMVF11, 100/475, 104E, amosite, crocidolite, and other SVF on TNF-α production in rat alveolar macrophages. MMVF10 and MMVF11 did not stimulate TNF-α production; whereas, the effects of 100/475 and 104E glass were intermediate. [No statistics were reported but values were less than twice the control values.] Values for amosite and crocidolite asbestos were about 2.5 to 3.2 times greater than controls. Fisher *et al.* (2000) investigated TNF-α production in four different cell types: primary rat alveolar macrophages, human peripheral blood monocytes, Thp-1 cells (derived from the peripheral blood of a 1-year-old boy with acute monocytic leukemia), and J774.2 cells (recloned from J774.1 cells which were recovered from a Balb C mouse). Fibers tested included amosite (35.3 % > 20 μm), 100/475 glass (19.3 % > 20μm), and MMVF10 (67.2 % > 20μm). Cells were incubated with the various fiber

types for 16 hours. None of the fiber types resulted in a significant increase in TNF-α production for any of the cell types. TNF-α release did not equate to fiber pathogenicity in this study.

The glass fiber-induced expression of TNF-α likely involves several different transcription factors, including NF-κB, which is involved in the activation of a variety of proinflammatory genes (Schins and Donaldson 2000). Mechanisms involved in NF-κB activation by fibers include reactive oxygen species, arachidonic acid metabolism, physiochemical properties of the fibers (e.g., fiber dimensions, transition metals), lipid peroxidation, and frustrated phagocytosis. Gilmour *et al.* (1997) reported that MMVF10 upregulated the nuclear translocation of AP-1 transcription factor in rat alveolar macrophages by about 12% compared with untreated controls but did not affect NF-κB. In the same study, AP-1 was upregulated by 37.4% and NF-κB by about 20% by amosite. Brown *et al.* (1999) investigated the effects of fiber exposure on NF-κB nuclear translocation in A549 human alveolar epithelial cells. Asbestos fibers caused a dose-dependent increase in NF-κB nuclear translocation, but MMVF10 and code 100/475 fibers did not. When the fiber dose was doubled from 8.24×10^6 to 16.48×10^6, MMVF10 caused a significant increase in the nuclear translocation of NF-κB. Doubling the dose of 100/475 fibers did not have an effect.

In other studies, a substantial increase in TNF-α production and the DNA-binding activity of NF-κB in RAW 264.7 mouse monocytes (Ye *et al.* 1999) and NR 8383 rat alveolar macrophages (Ye *et al.* 2001) was observed when exposed to code 100 fibers. These studies compared the effects of long fibers (17 μm) and short fibers (7 μm) after exposure for 3, 6, or 16 hours. TNF-α production was not induced after a 3-hour exposure, but a significant induction was observed after 6 or 16 hours. The TNF-α gene promoter was activated after exposure to both short and long fibers; however, the long fibers showed a 100% increase in stimulatory activity compared to short fibers. The increase in DNA binding activity of NF-κB indicated that this transcription factor was responsible for activation of the gene promoter. On a fiber-per-fiber basis, long glass

fibers were two to four times more potent than short fibers in inducing NF-κB, the gene promoter activity, and production of TNF-α.

Ye *et al.* (2001) also demonstrated that glass fibers induced phosphorylation of MAP kinases, p38, and ERK in primary rat alveolar macrophages exposed to code 100 fibers and that this phosphorylation was associated with TNF-α gene expression. When transcription factor inhibitors were included in the assays, release of TNF-α was almost completely inhibited by SN50 (an inhibitor of NF-κB), 70% by an inhibitor of p38, and 50% by an inhibitor of ERK. Xie *et al.* (2000) conducted a study to determine if TNF-α affected binding (defined as resistant to removal by a simple washing technique) of fibers to epithelial cells. Rat tracheal explants were exposed to TNF-α, or to culture medium alone, followed by a suspension of amosite or MMVF10. Exposure to TNF-α increased epithelial fiber binding, but higher TNF-α doses were needed to show an effect with MMVF10. This effect was abolished by an anti-TNF-α antibody and an NF-κB inhibitor indicating that fiber binding was controlled by a NF-κB–dependent mechanism.

Inflammation and fibrosis

Chronic inflammation also is known to be an important factor for fibrosis. In rodent inhalation studies of fibers and other particulates, lung cancer is almost always preceded by chronic inflammation and fibrosis (IARC 2002). Although high levels of pulmonary fibrosis have been found in studies showing significant lung tumor incidences, a direct cause and effect relationship has not been established (Kane 1996a). Nevertheless, IARC (2002) concluded that the proposed mechanistic links between chronic inflammation, fibrosis, and cancer are biologically plausible.

5.6.3 Genotoxic effects

Genotoxic effects include oxidized bases, DNA breaks, aneuploidy, and mutations and may result from three possible mechanisms: (1) direct interaction of fibers with the spindle apparatus, (2) release of fiber components that directly damage DNA, and (3) indirect damage resulting from chemical species released during chronic inflammation. As discussed previously (see Section 5.5.3, "*Chromosomal or chromatid-related effects*"), phagocytized fibers may interfere with chromosome segregation during mitosis. Some studies using light microscopy on fixed cells have suggested that long fibers can

interfere with the mitotic spindle, causing lagging chromosomes and subsequent aneuploidy (Kane 1996a). Aneuploidy, polyploidy, and binucleated cells have been observed in a wide variety of rodent and human cell types *in vitro*; however, it has not yet been established *in vivo* whether fibers are internalized by the target cells that are responsible for bronchogenic carcinoma or malignant mesothelioma.

Physical interference with chromosomal segregation is not the only way fibers might disrupt mitosis (Kane 1996a). Disruption of the cytoskeletal organization of the cell could enhance the interaction of fibers with the mitotic spindle, and interference with the cleavage furrow might result in binucleated daughter cells.

Johnson and Jaramillo (1997) examined expression of p53, Cip1, and Gadd153 proteins following treatment of A549 cells with crocidolite and JM100 fibers. These proteins are associated with DNA damage and cell-cycle arrest. A dose-dependent toxicity was observed with both fiber types, but the cytotoxic effects were more marked with JM100 when compared with crocidolite on an equal mass/unit area basis. There was a dose-dependent increase in expression of all three proteins in crocidolite-exposed cells but not with JM100 fibers. Pache *et al.* (1998) exposed a human mesothelial cell line (MET5A) or A549 cells to various concentrations of crocidolite and MMVF10 and measured the intensity and distribution of epidermal growth factor receptor (EGF-R) protein. Crocidolite asbestos, but not MMVF10, caused an increase in the number of EGF-R positive MET5A cells. No increase in EGF-R positive A549 cells was observed with either fiber type.

Most of the studies of DNA damage were conducted with target cell populations *in vitro*. Important factors include the fiber source and preparation, cell type, species, and assay conditions. Several natural and synthetic fibers (SVFs) have caused DNA damage in rodent and human cells. Studies with asbestos indicate that mesothelial cells may be more sensitive to DNA damage than epithelial cells or fibroblasts (Kane 1996a). Nguea *et al.* (2008) reviewed SVF-induced genotoxicity and reported that asbestos fibers (including amosite, chrysotile, and crocidolite) appeared to be more genotoxic that glass fibers based on higher levels of DNA base oxidation (i.e., 8-OHdG). *In vivo* studies using Big Blue transgenic rats indicated that glass fibers of low biopersistence were not mutagenic for

lung DNA (see Section 5.3); however, asbestos fibers caused an increase in mutant frequency (Bottin *et al.* 2003, Rihn *et al.* 2000). Although a number of studies (see Section 5.4.4) have shown that glass fibers can cause DNA damage, micronuclei, and chromosomal aberrations *in vitro*, relatively few *in vivo* studies have been conducted. The exact genotoxic mechanisms initiated and sustained by SVF are not well understood and further study is needed to distinguish between direct and indirect DNA damage (Greim 2004).

Schürkes *et al.* (2004) investigated the role of inflammation-driven genotoxicity in fiber-induced carcinogenesis (MMVF11 glass fibers and crocidolite) (see Section 5.4.1.3) and reported a correlation between parameters of inflammation with the induction of 8-OHdG.

5.6.4 Cytotoxicity and proliferation of target cells

High concentrations of asbestos fibers are toxic to target cell populations *in vitro*; however, under certain conditions, asbestos fibers induce cell proliferation (Kane 1996a). Kane (1996a) identified four potential mechanisms of growth stimulation based on studies with asbestos fibers. Each mechanism requires direct interaction with target cells and includes the following: (1) compensatory cell proliferation in response to toxicity, (2) stimulation of intracellular signal transduction pathways, (3) direct mitogenesis, and (4) induction of growth factor and growth factor receptor expression.

Cell proliferation

Cell proliferation is triggered as part of the healing response to tissue injury. Intraperitoneal injection of asbestos has caused injury to the mesothelial lining of the parietal pleura (diaphragm) in mice, and localized damage to the alveolar epithelium following inhalation or intratracheal administration is believed to facilitate translocation of fibers into the interstitium of the lungs (Kane 1996a). Hart *et al.* (1994) evaluated MvL 901 glass fibers and Blake *et al.* (1998) evaluated Code 100 glass fibers. Both studies showed length-related toxicity. Fibers of lengths 17 to 33 μm showed marked increases in toxicity, while fibers less than 7 μm in length showed significantly less, or no toxicity. Fiber thickness also had a modest effect on toxicity in one study. It was concluded that long fibers were toxic *per se*, in addition to their ability to accumulate in the lung due to

slower clearance rates. It was suggested that the increased toxicity of long fibers was due to frustrated phagocytosis leading to leakage of oxidants and enzymes.

Signal transduction pathways

Intracellular signal transduction pathways are commonly triggered in response to tumor promoters and asbestos fibers (Kane 1996a). Experimental evidence demonstrates that asbestos fibers can act as a tumor promoter, activate protein kinase C, cause increased expression of ornithine decarboxylase, and cause hydrolysis of inositol phospholipids.

Mitogenic effects

Evidence for the mitogenic effects of fibers is based on *in vitro* studies that show induction of the proto-oncogenes *c-fos* and *c-jun* following exposure to asbestos (Gao *et al.* 1997, Janssen *et al.* 1994). Prolonged expression of proto-oncogenes may result in growth stimulation of target cells.

The induction of proto-oncogenes (Gao *et al.* 1997, Janssen *et al.* 1994), expression of DNA damage-inducible genes (Johnson and Jaramillo 1997), and epidermal growth factor-receptor (Pache *et al.* 1998) by glass wool have also been investigated. Janssen *et al.* (1994) examined the effects of crocidolite, chrysotile, MMVF10 and other fibers and particulates on mRNA levels of *c-fos*, *c-jun*, and ornithine decarboxylase in hamster tracheal epithelial (HTE) cells and rat pleural mesothelial (RPM) cells. These cells were selected because they are the progenitor cells of bronchogenic carcinoma and mesothelioma, respectively. MMVF10 was less cytotoxic than asbestos and RPM cells were more susceptible to cytotoxicity than HTE cells. There was an increase in *c-jun* mRNA levels in HTE cells after exposure to asbestos or MMVF10; however, the increases were lower after exposure to MMVF10 compared with asbestos. No alterations in *c-fos* levels mRNA levels were observed in HTE cells. Ornithine decarboxylase mRNA levels also were increased in HTE cells after exposure to asbestos or MMVF10. Crocidolite asbestos caused increases in *c-fos*, *c-jun*, and ornithine decarboxylase in RPM cells, but MMVF10 did not when added at nontoxic concentrations (<10 $\mu g/cm^2$). At a higher concentration of MMVF10 (25 $\mu g/cm^2$), *c-fos* and *c-jun* mRNA levels were increased. Gao *et al.* (1997) investigated the relationship between silica and glass fiber-induced cell transformation and oncoprotein expression (protein products from seven

proto-oncogenes), and p53 in BALB/c-3T3 cells. All transformants induced by glass fibers were positive for *c-jun* protein expression. The other proto-oncogene proteins or tumor suppressor genes (c-K-*ras*, c-H-*ras*, c-*myc*, c-*sis*, c-*erb* B1, c-*myb*, and p53) were either not detectable or were not significantly different between transformed and non-transformed cells.

Growth factors

Increased expression of platelet-derived growth factor (PDGF-AA) and its receptor was demonstrated *in vitro* in rat lung fibroblasts exposed to asbestos fibers (Lasky *et al.* 1995). Increased expression of growth factors and their receptors may trigger cell proliferation by activating an autocrine growth-stimulatory pathway. However, the mechanism responsible for turning on transcription factors that regulate specific genes has not been identified. One possibility is oxidant stress from generation of ROS and activation of NF-κB.

Cytotoxicity

Nguea *et al.* (2005) reported that cell viability was inversely related to fiber concentration regardless of the type and size of fibers. These authors concluded that cell overloading may be responsible for the cytotoxicity of fibers because cytotoxicity was observed only when the ratio of fibers to cells was high. Castranova *et al.* (1996) reported that long and thick fibers designed for building insulation had only a weak effect on cell viability of rat alveolar macrophages and did not affect macrophage function.

Extracellular release of cytoplasmic lactate dehydrogenase (LDH) and beta-glucuronidase (BGU) can cause cytotoxicity (Nguea *et al.* 2008). Release of LDH indicates loss of membrane integrity, and BGU is a lysosomal enzyme biomarker of phagocyte damage or activation. Castranova *et al.* (1996) reported that glass microfibers induced a dose-dependent release of both LDH and BGU from rat alveolar macrophages. Blake *et al.* (1998) reported that cytotoxicity in rat alveolar macrophages was directly related to glass fiber length over 17 μm; however, chemical composition also had some influence.

5.6.5 Co-carcinogenesis

Lung cancer risk is enhanced in asbestos workers who smoke (Hesterberg and Hart 2001). Although a small excess of lung cancer occurs in non-smokers exposed to

asbestos, most cases of lung cancer occur in people exposed to asbestos who are smokers (Kane *et al.* 1996b). It is not known if the mechanisms leading to lung cancer are the same for smokers and non-smokers exposed to asbestos. However, there is experimental evidence that asbestos fibers enhance the delivery of the carcinogens in cigarette smoke and increase their metabolic activation (Kane 1996a). Furthermore, cigarette smoking reduces ciliary action in the tracheobronchial region and enhances fiber penetration into the bronchial epithelium.

Exposure to SVFs generally consists of a mixture of non-fibrous and fibrous particulates. Several of the mechanisms described in this section (e.g., cell proliferation and chronic inflammation) are responses to particulate exposure in general and not just to fibers. Little is known about the interactions of fibers with non-fibrous particles, particularly the less toxic particulates. However, increased incidences of lung tumors and mesotheliomas have been reported in rats exposed by inhalation to a mixture of chrysotile asbestos and non-fibrous dust (Kane 1996a).

Another possible, yet controversial, co-carcinogenic interaction is with SV40 virus. SV40-like DNA sequences have been identified in human mesothelioma tissue samples but not in adjacent lung tissue (Carbone *et al.* 1994, Rivera *et al.* 2008). The origin of the viral DNA and its relationship to malignant mesothelioma is unknown. The viral oncoprotein can bind to p53 and inhibit its activity (IARC 1999). Rivera *et al.* (2008) reported that co-carcinogenesis between SV40 and asbestos in causing malignant mesothelioma has been demonstrated in three separate laboratories using different experimental approaches; however, epidemiological evidence is lacking due to unattainable identification of infected from noninfected cohorts.

5.7 Summary

5.7.1 Deposition, clearance, and retention

Fibers that are carried in the inhaled air to the tracheobronchial region are considered *inhalable* while those that reach the alveolar region are considered *respirable*. Fibers that are inhalable but non-respirable can deposit in the extrathoracic and tracheobronchial regions and can cause adverse effects. Deposition refers to the actual dose deposited in the lung and is influenced by the anatomy and physiology of the airway, respiratory rate,

and physical properties of the fiber. Deposition occurs by impaction, sedimentation, interception, and diffusion. Peak deposition occurs in rodents and humans for fibers with aerodynamic diameters of 1 to 2 μm.

Clearance and retention of fibers are affected by chemical composition, size distribution, number of fibers deposited, and time since last exposure. Clearance mechanisms also depend on the region of deposition. Short fibers are readily phagocytized by alveolar macrophages and transported from the lower lung to the upper airways and cleared through the mucociliary escalator. Long fibers are resistant to phagocytosis, but depending on the fiber type, may be subject to dissolution and transverse breakage. Particle overload (which has been observed in rats) occurs when the deposition rate of poorly-soluble, low cytotoxic particles exceeds the normal clearance rate, and can result in adverse effects.

5.7.2 *Biodurability and biopersistence of glass fibers*

Biodurability describes the rate of removal through dissolution or disintegration; biopersistence includes biodurability plus physiological clearance and refers to the capacity of a fiber to persist and to conserve its chemical and physical features over time in the lung. Biodurability is expected to be similar in rats and humans, but biopersistence may be substantially different due to differences in the physiological clearance mechanisms. In general, biodurability of various fibers in the lung has been ranked as follows: glass fibers < refractory ceramic fibers < chrysotile asbestos < amphibole asbestos. Highly durable fibers, such as asbestos, are resistant to dissolution and transverse breakage. Although experimental dissolution rates for glass fibers show variability (up to a 30-fold range), they generally show some correlation with clearance rates of long fibers in short-term biopersistence studies. Certain components of SVFs are subject to leaching resulting in changes in composition over time. The fibers become weaker from fractures, peeling, and pitting and may break.

5.7.3 Toxic effects

Several studies have evaluated mortality from non-malignant respiratory disease or morbidity related to the respiratory system among workers exposed to glass wool. A significantly elevated SMR for non-malignant respiratory disease was found in the earlier

updates, but not the most recent update of the large U.S. cohort study. Mixed findings have also been observed for adverse respiratory symptoms, pulmonary function, and lung abnormalities (detected on chest radiographs); workers in some studies were also exposed to asbestos.

Various types of glass wool fibers (MMVF10, MMVF11, 104E glass fibers, JM100/475 microfibers) caused adverse lung effects (such as inflammation and fibrosis) in rats exposed by inhalation (Hesterberg *et al.* 1993, 2002, Cullen *et al.* 1990, Bellmann e*t al.* 2003, Bermudez *et al.* 2003). In hamsters, inhalation of MMVF10 fibers caused inflammatory effects, but not fibrosis (Hesterberg *et al.* 1993, Bermudez *et al.* 2003). In cytotoxicity studies, longer fibers induced greater toxicity in rat alveolar macrophages (Blake *et al. 1*998, Hurst *et al.* 1994).

5.7.4 Genetic and related effects

Glass fibers were shown to induce production of reactive oxygen species in cell-free systems and cultured cells, to damage DNA, and to cause chromosomal aberrations, nuclear abnormalities, mutations, gene amplification in proto-oncogenes, and cell transformation in mammalian cells. However, glass wool fibers did not cause mutations in bacteria or cause sister chromatid exchange in mammalian cells, but only two types of fibers were tested in each of these assays. Glass wool fibers also induced DNA strand breaks (measured by the comet assay) in macrophages and lung epithelial cells, and oxidative stress in rats, but did not induce mutations *in vivo*. Further, fiber persistence may also lead to inflammation-driven (indirect) genotoxicity, as reactive inflammatory cells release reactive oxygen species, growth factors, and cytokines. Fiber characteristics did not appear to be important in the production of reactive oxygen species, and studies assessing oxidative damage by different endpoints were positive for both special-purpose fibers and insulation glass wool fibers. Similarly, fibers of different lengths and diameters were able to cause DNA damage in mammalian cells. However, effects on chromosomes and nuclear abnormalities may be related to fiber characteristics; longer fibers appeared to be more potent in causing these genotoxic effects. Some studies suggested that thinner fibers were also more effective. Results from cell transformation studies also suggested that longer and thinner fibers produced higher transformation efficiency.

5.7.5 Mechanisms of fiber carcinogenicity

Several investigators have evaluated fiber characteristics (dimensions and durability or biopersistence) and tumorigenicity in studies in experimental animals. These studies (by intraperitoneal injection and intrathoracic implantation) show that fiber dimensions and durability were important determinants of tumorigenicity. In intrathoracic implantation studies, pleural sarcomas were correlated with fiber dimensions; long thin fibers were associated with the highest tumor incidence. Fibers with a high dissolution rate tended to have a low potency in the intraperitoneal assay. A relationship between biopersistence in the lung and pathology was also observed in inhalation studies in rats. Clearance half-times of long fibers (> 20 μm) were approximately 400 to 800 days for two types of asbestos, 80 days for E glass, 50 days for JM100/475 glass, 15 days for MMVF10, and 9 days for MMVF11.

The major proposed mechanisms of fiber-induced carcinogenicity are related to the physical and chemical properties (such as size or dimensions, durability, surface reactivity, and chemical composition) of the fibers and to the inflammatory response that results from the inhalation of fibers. Fiber size affects deposition and clearance, and biodurabilty and biospersistence are related to biological effects. Fibers can directly interact with target cells (epithelial cells, mesothelial cells, fibroblasts) leading to an inflammatory response and/or genotoxicity. Fibers may induce genotoxic effects by interacting with the spindle apparatus of chromosomes, directly damaging DNA or indirectly damaging DNA through chronic inflammation. Alveolar macrophages are activated in response to particulates or fibers deposited in the lung, resulting in increased release of reactive oxygen species, chemical mediators, and cytokines (such as TNF-α) and activation of signalling pathways. A sustained inflammatory reaction may result from incomplete phagocytosis (frustrated macrophages) and prolonged interaction of persistent fibers with the cell surface. Chronic imbalance between cytokines and growth factors may contribute to tissue injury, proliferation, and/or apoptosis, which may lead to fibrosis and tumors.

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Glossary of Terms

Acute: The clinical term is used for a disease having a short and relatively severe course. In rodent testing, usually pertains to administration of an agent in a single dose.

Adduct: A complex that forms when a chemical binds to a biological molecule such as DNA or a protein.

Adenocarcinomas: A cancer that develops in the lining or inner surface of an organ.

Adenoma: An ordinarily benign neoplasm of epithelial tissue in which the neoplastic cells form glands or gland-like structures in the stroma.

Aerodynamic diameter: A physical property of a particle or fiber in a viscous fluid such as air. In general, particles have irregular shapes with actual geometric diameters that are difficult to measure. The equivalent aerodynamic diameter is defined as the diameter of a spherical particle of unit density which has the same terminal settling velocity in still air as the particle or fiber in question.

Allele: Any one of a series of two or more different genes that occupy the same position (locus) on a chromosome.

Alveolar/bronchiolar: Pertaining to the alveoli or bronchi of the lungs.

Ambient air: Outdoor air to which the general public is exposed.

Aneuploidy: One or a few chromosomes above or below the normal chromosome number.

Apoptosis: Cell deletion by fragmentation into membrane-bound particles which are phagocytosed by other cells.

Aromatic hydrocarbon: An organic chemical compound formed primarily from carbon and hydrogen atoms with a structure based on benzene rings and resembling benzene in chemical behavior; substituents on the rings(s) may contain atoms other than carbon or hydrogen.

Aspect ratio: The ratio of fibers' length to diameter.

Assay: is a procedure where a property or concentration of an analyte is measured.

Batt: Precut panels of insulation available in a variety of widths, lengths, and R-values.

Benign tumor: An abnormal mass of tissue that does not spread and that is not life-threatening.

Bioaccumulation: The process by which a material in an organism's environment progressively concentrates within the organism.

Biodegradation: Biotransformation; the conversion within an organism of molecules from one form to another. A change often associated with change in pharmacologic activity.

Biopersistence: The ability of a fiber to remain in the lung. Biopersistence is a function of the fiber solubility and the biological ability of the lung to clear the fiber.

Bronchiolization: a process of migrating bronchiolar cells progressively colonizing alveolar spaces.

Bronchioloalveolar: Derived from epithelium of terminal bronchioles.

Bronchoalveolar lavage: A technique used to obtain a sample of the cells, fluids, and other materials present in the very small airways and alveoli of the lung by instilling saline into the airway via a bronchoscope.

Carcinoma: A malignant neoplasm of the epithelium.

Chromosomal aberrations: Any abnormality of a chromosome's number or structure.

Chronic: Continuing for a long period time. In rodent testing, pertains to dosing schedules of greater than 3 months.

Clastogen: Any substance which causes chromosomal breaks.

Clearance rate: The rate at which deposited particles are removed by various processes from the respiratory tract. Both the fiber's physical and chemical characteristics affect the clearance rate.

Confounding: A relationship between the effects of two or more causal factors observed in a set of data such that it is not logically possible to separate the contribution of any single causal factor to the observed effects.

Continuous glass filament: An extruded filament usually having a relatively large diameter (greater than 6 μm) and a very narrow range of diameter distribution.

Dehydrogenation: The removal of one or more hydrogen ions or protons from a molecule.

Density: The density for solids and liquids is expressed in grams per cubic centimeter (g/cm^3) and is generally assumed to refer to temperatures near room temperature unless otherwise stated. Values for gases are generally the calculated ideal gas densities in grams per liter at 25°C and 101.325 kPa.

Diffusion: One of four mechanisms of fiber deposition in the respiratory tract (see also impaction, sedimentation, and interception). Deposition by diffusion is especially important for smaller particles. As particles decrease in size, thermodynamic properties prevail over aerodynamic properties, and for particles < 0.5 μm,

deposition and is governed mainly by the diffusional movement induced by Brownian motion of gas molecules.

Diffusion coefficient: The rate at which a substance moves from an area of high concentration to an area of low concentration.

Endogenous: Originating within an organism.

Epidemiology: A science concerned with the occurrence and distribution of disease in populations.

Epithelial: Relating to or consisting of epithelium.

Ferruginous body: A mineral particle to which pulmonary macrophages have added an iron protein coat. Ferruginous bodies are used as an indicator of exposure to specific dusts or fibers.

Fiber: A particle with a length to width ratio of at least 3:1

Flux: Another term used for a modifier in the glass wool manufacturing process. Typically, oxides such as magnesium oxide (magnesia, MgO), lithium oxide (Lithia, Li2O), barium oxide (baria, BaO), calcium oxide (calcia, CaO), sodium oxide (soda, Na2O) and potassium oxide (K2O) are used as fluxes.

Fibroblasts: Connective tissue cells.

Genotoxicity: The amount of damage caused to a DNA molecule.

Glass fiber: General term that may be used to refer to reinforcing glass filament, glass wool, or superfine glass fiber.

Glass wool: A fibrous product formed by blowing or spinning molten glass. The resultant fibers are collected as a tangled mat of fibrous product.

Hematopoietic: Pertaining to the formation of blood or blood cells.

Half-life: The time required for a substance to be reduced to one-half its present value through degradation or through elimination from an organism.

Hodgkin's disease: A form of malignant lymphoma characterized by painless progressive enlargement of the lymph nodes, spleen, and general lymphoid tissue.

Homozygotes: An organism that has the same alleles at a particular gene locus on homologous chromosomes.

Hydrolysis: The chemical breakdown of a compound due to reaction with water.

Hydroxyl radicals: A particularly reactive, damaging type of free radical that is formed when superoxide radicals react with hydrogen peroxide.

ICD: The International Classification of Diseases. Published by World Health Organization, ICD codes are specific three-character codes used to describe a patient's health care condition.

Impaction: One of four mechanisms of fiber deposition in the respiratory tract (see also sedimentation, diffusion, and interception). Deposition by impaction occurs when the airflow encounters rapid changes in direction and the momentum of the fiber carries it along in a straight line to deposit on the airway wall. The larger the aerodynamic diameter, the greater the deposition efficiency due to impaction. This mechanism is most effective for aerodynamic diameters 0.5–1.0 µm.

***In vitro*:** Biological process taking place in a test tube: Culture dish: Or elsewhere outside a living organism.

***In vivo*:** Biological processes taking place in a living organism.

Interception: One of four mechanisms of fiber deposition in the respiratory tract (see also impaction, diffusion, and sedimentation). Deposition by interception occurs when an airborne fibre in the airway gets close enough to the airway wall to allow one end to touch the wall. For an elongated object such as a fibre, this occurs more readily than for a spherical particle, and thus, interception is a particularly important mechanism for fibre deposition, especially for longer fibers.

Intraperitoneal [i.p.] injection: Injection within the peritoneal cavity, i.e., the area that contains the abdominal organs.

Leukemia: A cancer of the blood-forming tissues that is characterized by a marked increase in the number of abnormal white blood cells (leukocytes).

Lymphatic: A small sac or node in which lymph is stored; or pertaining to the lymph, lymph nodes, or vascular channels that transport lymph to the lymph nodes.

Lymphohaematopoietic: Of, relating to, or involved in the production of lymphocytes and cells of blood, bone marrow, spleen, lymph nodes, and thymus.

Lymphoma: A neoplasm of the lymphatic tissue.

Lymphosarcoma: Any of various malignant neoplastic disorders of lymphoid tissue; excluding Hodgkin's disease.

Macrophage: A large cell that is present in blood, lymph, and connective tissues, removing waste products, harmful microorganisms, and foreign material from the bloodstream.

Malignant: Tending to become progressively worse; life-threatening.

Mesothelioma: Cancer of the mesothelium a lining covering most internal organs.

Metabolism: The whole range of biochemical processes that occur within living organisms, consisting both of anabolism and catabolism (the buildup and breakdown of substances, respectively).

Metabolite: A substance produced by metabolism.

Micronuclei: Nuclei separate from, and additional to, the main nucleus of a cell, produced during the telophase of mitosis or meiosis by lagging chromosomes or chromosome fragments derived from spontaneous or experimentally induced chromosomal structural changes.

Mineral wool: May refer to either slag wool or rock wool depending on the raw material from which it is produced.

Multiple myeloma: A malignant neoplasm derived from plasma cells and found at several locations in the body.

Necropsy: The examination of the dead body of an animal by dissection so as to detail the effects of the disease.

Necrosis: The pathologic death of one or more cells, or of a portion of tissue or organ, resulting from irreversible damage.

Neoplasm: An abnormal mass of cells.

Non-Hodgkin's lymphoma: A heterogeneous group of malignant lymphomas; the only common feature being an absence of the giant Reed-Sternberg cells characteristic of Hodgkin's disease.

Odds Ratio: The odds ratio is a way of comparing whether the probability of a certain event is the same for two groups. It is often used as a statistical measure of the likelihood of developing a disease if a certain factor – such as exposure to an agent.

Parenchyma: The distinguishing or specific cells of a gland or organ, contained in and supported by the connective tissue, framework, or stroma.

Pledget: a small plug.

Resin: Any of numerous physically similar polymerized synthetics or chemically modified natural resins..

Respirability: The relative amount of airborne particles or fibers reaching the alveolar region of the lung.

Respirable fiber: These fibers can reach the deepest part of the lung. For humans, respirable fibers are defined as particles with a diameter less than 3 μm and length

greater than 5 μm and with an aspect ratio of greater than 3:1. These fibers can reach the deepest part of the lung.

Respirable fraction: That portion of dust or fibers that can reach the lower, or gas exchange, part of the respiratory system.

Sarcoma: Cancer of connective tissue; can also refer to tumors in soft tissue.

Sedimentation: One of four mechanisms of fiber deposition in the respiratory tract (see also impaction, diffusion, and interception). Sedimentation refers to the settling of fibers due to gravitational forces, which eventually results in the fibers touching the airway wall and depositing on the epithelium. This mechanism operates mainly on fibers with aerodynamic diameters of 0.5–1.0 μm.

Sister chromatid exchange (SCE): The exchange during mitosis of homologous genetic material between sister chromatids; increased as a result of inordinate chromosomal fragility due to genetic or environmental factors.

Slag wool: a fibrous product manufactured by blowing or spinning of a molten mass of metallurgical furnace slag.

Standardized Incidence Ratio (SIR): The ratio of observed to expected new incidences of a specific health outcome (e.g., cancer). The figure for expected incidence reflects the number of incidences for the larger population from which the study sample has been taken e.g., national level incidences.

Standardized Mortality Ratio (SMR): The ratio of observed to expected deaths to a specific health outcome (e.g., cancer). The figure for expected deaths reflects the number of deaths for the larger population from which the study sample has been taken e.g., national level of mortality attributed to a particular health outcome.

Stanton fibers: Fibers with length > 8 μm and diameter ≤ 0.25 μm.

Subacute: Between acute and chronic; denoting the course of a disease of moderate duration or severity. In rodent testing, usually pertains to a dosing schedule of less than one month.

Subchronic: In rodent testing, generally refers to a dosing schedule lasting from one to three months.

Subcutaneous injection: Injection beneath the skin.

Threshold limit value (TLV): The maximum permissible concentration of a material, generally expressed in parts per million in air for some defined period of time.

Time-weighted average (TWA): The average exposure concentration of a chemical measured over a period of time (not an instantaneous concentration).

Volatile: Quality of a solid or liquid allowing it to pass into the vapor state.

Xenobiotic: A pharmacologically, endocrinologically, or toxicologically active substance not endogenously produced and therefore foreign to an organism.

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